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H. Willoughby Lyle.

A SYSTEM OF MEDICINE

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BY MANY WRITERS

EDITED BY

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PREFACE

As announced in the first volume the original second volume of the *System of Medicine* will now be represented by two parts; this part contains the continuation of the Infections and the Intoxications, together with an important article on the General Pathology of Infection, by Professor James Ritchie. The Tropical Diseases have been removed from their positions in the first edition and collected, together with the Animal Parasites, into a single volume, which, since it contains many subjects originally treated in the second volume of the first edition, may be conveniently brought out at the same time as this revised instalment. It is, however, so much expanded in scope as to constitute a new rather than a revised or rewritten volume of the *System of Medicine.*

The advances of ten years have obliged Professor Ritchie to rewrite the article on the General Pathology of Infection, originally contributed by the late Professor Kanthack, almost entirely; and have necessitated a more liberal allowance of space. Some of the additions and changes in the arrangement may be briefly chronicled. A new article on the Pathology of the Streptothrix Infections by Mr. Foulerton, has been added to Dr. Acland's contribution on Actinomycosis. Syphilis has been transferred from the "Infectious Diseases of Uncertain Bacteriology" to the "Chronic Infections of Established Bacteriology." Rheumatic fever has been brought from Volume III., where it appeared in conjunction with Rheumatoid Arthritis, under "General Diseases of Obscure Origin," to the "Infectious Diseases of Doubtful Origin," and has been supplemented by an account of its bacteriological relations by Dr. W. Bulloch.

The difficult subject of a "common cold" has been handled by Dr. Dawson Williams. The authorship of the revised articles has fortunately required comparatively little change; for the late Mr. Ernest Hart's article on vaccination as a branch of Preventive Medicine, an authoritative contribution from Dr. J. C. M'Vail has been substituted. In the Article on Anthrax, Dr. Legge, H.M. Medical Inspector of Factories, entered into collaboration with Dr. Bell, whose lamented death occurred only a few months after he had completed this revision. Dr. Sidney Martin, restrained by his seat on the Royal Commission, has been unable to revise his article on Tuberculosis, but this task has been carried through, at rather short notice, by Dr. Bosanquet. A new article on Food Poisoning has been provided by Dr. Batty Shaw.

T. C. A.
H. D. R.

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In order to avoid frequent interruption of the text, the numbers indicative of items in the lists of "References" are only inserted in cases of emphasis, where two or more references to one author are in the list, where an author is quoted from a work published under another name, or where an authoritative statement is made without mention of the author's name. In ordinary cases an author's name is sufficient indication of the corresponding item in the list.

THE GENERAL PATHOLOGY OF INFECTION

By Prof. James Ritchie, M.D.

Introductory.—The study of the pathology of infection in the widest and most scientific sense of the word is almost, if not quite, conterminous with the study of the effects of any foreign living agent when it gains a foothold—and especially when it multiplies—in the animal body. Another great truth has also emerged in modern times in the recognition of the fact that notwithstanding the diversity of clinical types produced by different agents, there is a great unity in the morbid processes set up. We must therefore, in taking a broad view of the subject, be prepared to account for observed facts, and to recognise common processes in such varied conditions as the following:—

(1) The action of parasitic fungi and bacteria in such diseases as favus, septicæmia, tuberculosis, diphtheria, enteric fever, etc.

(2) The action of parasitic protozoa in such diseases as malaria, tsetse-fly disease, etc.

(3) The action of what for the present are called "ultra-microscopic" living agents in such diseases as pleuro-pneumonia and foot-and-mouth disease in cattle, and probably yellow fever in man.

(4) The action of parasites of unknown character, though probably belonging to one or other of the last three groups, which are in all likelihood associated with such diseases as small-pox, scarlet fever, hydrophobia, measles, and so forth.

(5) It is a question whether certain phenomena associated with the presence of parasitic worms in the body ought not properly to be classed along with the phenomena of undoubted infections.

Most of our knowledge regarding the pathology of infection has been derived from the study of the bacterial infections of known origin, and in the following article these will form the chief basis for discussion.

It is unnecessary to enter into any details regarding the morphology

and biology of the bacteria. These organisms, from the structural standpoint, represent the lowest type of living matter, the characteristics of each species being, generally speaking, summed up in the vital capacities of a single cell. This at any rate is true of the lower bacteria, which include nearly all the pathogenetic forms. These are divided, according to their shape, into the three groups of the cocci, the bacilli, and the spirilla; they multiply by simple fission; some bacillary and spirillary forms are motile, and in some bacilli the protoplasm may, under certain conditions, develop into a spore, and it is then highly resistant to the action of external agents, such as heat, antiseptics, etc. A few pathogenetic forms (chiefly streptothrices, *e.g.* streptothrix actinomyces) belong to the higher bacteria; these organisms have a filamentous character (the filaments being made up of units resembling the lower bacteria in form), and here there is more interdependence between the units composing the filaments.

I. The Relations of Bacteria to Disease

The Biology of the Bacteria in Relation to Disease.—While the bacteria are structurally simple, their protoplasm is as capable of complex activity as that of any other form of life. The chief part played by bacteria in nature is in connexion with putrefaction. Most bacteria find their food in the dead bodies of plants or animals, or their excreta, and so far bacteria are saprophytes. From the pathological aspect, however, the most important point with regard to the food-supply of bacteria is that it may be furnished in the body of a living animal. Infective bacterial disease depends on the capacity of certain bacteria to live and multiply in the tissues of the body. As primitive animal cells depended for their nourishment on albuminous material previously elaborated by plants, the way was opened for the development of parasitic tendencies by living plants thus ingested, and there is no doubt that very early such parasitism arose. It is thus possible that the pathogenetic bacteria have all originally been derived from non-pathogenetic forms. And as in origin there is probably no difference between parasitic and saprophytic forms, so it is impossible to draw a hard-and-fast line between parasitic and saprophytic bacteria as they exist at present.

Thus organisms which, though usually occurring in the bodies of animals, can be grown in or on the usual laboratory media are not obligatory parasites, for they possess the faculty of living on dead matter outside the animal body.

This truth is of the utmost importance in the etiology, prevention, and hygienic treatment of infective diseases. We know very little of the natural life and habitat of most pathogenetic organisms; and often when we argue that certain infective organisms cannot find suitable conditions for growth outside the animal body, we may be arguing from ignorance. More than one organism, once thought to be strictly a parasite, is now recognised to be sometimes a saprophyte. The tubercle

bacillus, for instance, grows well on ordinary potatoes and on bread at the ordinary room temperature and at blood-heat; it is certainly therefore a facultative saprophyte. Moreover, it is very probable that many pathogenetic bacteria, such, for instance, as the tetanus bacillus, usually live a saprophytic existence, and gain entrance as parasites to the animal body only occasionally. Again, although some organisms, usually saprophytic in nature, produce disease when they gain entrance into the body by accident or experiment, in many cases saprophytes may be introduced without giving rise to any changes whatever. Several factors —such as unwonted temperature and food supply—may be concerned in this, but we shall see, when considering the question of immunity, that the occurrence opens up very deep problems concerning the mutual reactions of cells of different kinds.

The Bacteria associated with Disease Processes.—The following are the *chief* bacteria concerned with disease. With few exceptions they have been isolated and grown in pure culture.

A. LOWER BACTERIA.

Cocci.—*Staphylococcus pyogenes aureus* (also vars. *albus*, *citreus*, *flavus*, *cereus albus*, *cereus flavus*), *Streptococcus pyogenes* (also var. *erysipelatis*), *Pneumococcus*, *Gonococcus*, *Micrococcus melitensis*, *Diplococcus intracellularis meningitidis*.

Bacilli.—*Bacillus anthracis*, *Bacillus pestis*, *Bacillus typhosus*, *Bacillus coli*, *Bacillus dysenteriæ* (Shiga), *Bacillus influenzæ*, *Bacillus diphtheriæ*, *Bacillus tetani*, *Bacillus œdematis maligni*, *Bacillus tuberculosis*, *Bacillus lepræ*, *Bacillus mallei*.

Spirilla.—*Vibrio choleræ*.

B. HIGHER BACTERIA.—*Streptothrix actinomyces*, *Streptothrix maduræ*.

The Recognition of a Bacterium as the Cause of a Disease.—The nature of the evidence for a bacterium as the cause of a given disease varies in different instances. In some cases the proof is absolute, in others it is comparatively incomplete; to be rigorous, the following conditions must be fulfilled: (*a*) the bacterium must be invariably found in the tissues of an animal dead from or affected with the disease in question; (*b*) it must never occur in other diseases or in normal tissues; (*c*) the organism transmitted from the diseased or dead animal to an unaffected animal of the same species must produce lesions similar to those present in the animal from which it was derived, and in this second diseased animal the original organism must be found; (*d*) if the organism can be cultivated outside the animal body, then an artificial cultivation inoculated experimentally into an animal must again produce the disease, and this animal must again contain the organism in its tissues or blood; (*e*) it is an additional link in the chain of evidence when toxins having a specific action can be isolated from cultures of the

bacterium, and when these reproduce in animals the characteristic features of infection with the living organisms; (*f*) these processes must occur in invariable succession under identical conditions.

In human diseases it is of course rarely possible to establish the causal relationship between a bacterium and a disease by strictly following these canons. But a practically certain proof is attainable in such cases by establishing canons (*a*) and (*b*), by then reproducing the disease in animals and satisfying the remaining canons in the experimental inoculations. This is what has happened in the case of tuberculosis. The tubercle bacillus has been found in practically every manifestation of human tuberculosis. Pieces of such tuberculous tissues, or pure cultures isolated from these tissues, have been used in inoculation experiments, and have set up in animals lesions identical with some form of the human disease. From these lesions the bacillus has again been recovered. The more the effects produced in animals differ from those obtaining in man the greater care must be exercised in drawing conclusions, and the difficulty of the situation may be further increased by the non-specific nature of the lesions of the original disease. A good example is found in pneumonia. In man there is usually a lesion strictly confined to the lung. This lesion is, however, merely a particular type of an ordinary inflammation, such as occurs associated with many organisms. It is true that from the great majority of cases of pneumonia a specific bacterium—the pneumococcus—can be isolated. When this organism is injected into an animal, such as the rabbit, it will produce, even if inoculation into the lung be practised, not a pneumonia but a general septicæmia, characterised by a distribution of the bacteria all over the body, with, it may be, a tendency to local purulent serous inflammation. If, however, an intrapulmonary inoculation be practised in the sheep, then, as Gamaleia (132) has shewn, a condition practically identical with the human lesion is produced. There is thus little doubt that the organism is the cause of pneumonia in man, and this conclusion is supported by the very interesting cases of serous inflammations which occur from time to time, especially in children, and from which the pneumococcus has been isolated.

The Evidence that particular Bacteria are Morbific Agents.—Having given a list of the chief bacteria isolated from human infective disease, we shall now give in brief outline the nature of the evidence on which their etiological relation to the different diseases rests. (1) In the case of some bacteria the proof may be said to be absolute, since inoculations of human beings with pure cultures have been followed by the appearance of characteristic signs of the corresponding disease. This is true of the *Staphylococcus pyogenes aureus* in its relationship to boils. Such a lesion was produced by a bacteriologist rubbing a pure culture into his own arm after the skin had been sterilised. The same is true of the erysipelas variety of the *Streptococcus pyogenes*. The supposed effect of erysipelas in promoting the disappearance of malignant tumours justified Fehleisen (120) in injecting into patients pure cultures of this organism named, and in the cases so treated the disease resulted. Again,

that the gonococcus is the cause of gonorrhœa has been proved by inoculations in man by Bumm (61).

(2) There are several human diseases the bacterial etiology of which has been substantiated accidentally. Of these the chief are typhoid fever, cholera, plague, Malta fever. In the cases of the first two the evidence derivable from animal experiment is unsatisfactory. Under natural conditions of infection animals do not suffer from either disease; injection of animals with the bacteria isolated from man is not followed by the characteristic signs of the human disease, and subcutaneous inoculation with laboratory cultures often produces no disease whatever. With intra-peritoneal inoculation, however, there is usually comparatively rapid death in, say, from a few hours to some days, with some peritonitis and a semi-purulent exudation. In the case of the typhoid bacillus a condition somewhat resembling the natural disease has been produced by Sanarelli (303), who found that if the bacilli were injected into an animal, together with toxins derived from the bacillus coli, appearances suggestive of early typhoid fever appeared in the intestine. In the case of cholera the nearest approach to an imitation of the natural disease occurred in the experiments of Koch (162). This observer injected the vibrios into the stomach, having first neutralised the gastric juice with sodium carbonate; further, by paralysing the intestinal peristalsis with opium, he ensured that the organism should remain a sufficient time in the bowel to produce its toxic effects. The animals in many cases presented symptoms closely resembling cholera in man. But neither in the case of typhoid fever nor of cholera was the proof absolutely convincing. It has happened, however, that bacteriologists have accidentally swallowed pure cultures of the organisms, and have subsequently developed the corresponding disease. In the case of cholera, a number of intentional feeding experiments have also been performed by bacteriologists on themselves, and have been followed by choleraic symptoms. In the case of plague, animal experiments reproduce pathological conditions practically identical with the types of the disease found in man: but here, again, accidental inoculations with cultures in man have been followed by the development of the disease. In the case of Malta fever, bacteriologists who could not have been infected by ordinary channels, but who were working with pure cultures, have become infected with the disease. Although in such accidental inoculations in man the conditions of scientific experiment were not rigorously fulfilled, the results furnish a presumptive proof of the causal relationship of the bacteria to the disease which is little short of absolute.

(3) In by far the greater number of diseases in man from which certain bacteria have uniformly been isolated, the proof that these are really the causes of the corresponding affections rests on evidence derived from parallels between the lesions of the natural diseases in man and the lesions produced under rigid experimental conditions in animals. Such is the case with many of the inflammatory and suppurative diseases from which various organisms enumerated above have been isolated;

it is the case with the more slowly developing or chronic inflammations characteristic of tuberculosis in all its manifestations, with glanders, actinomycosis, anthrax, influenza, diphtheria, and tetanus. Frequently, as in the case of the last two diseases, the parallelism between the natural lesions in man and the artificial disease in animals is very close. In other cases, as in that of the pneumococcus already discussed, the results of the inoculation of some species of animals differ much from the effects produced in man, and a special line of interpretation must be adopted.

(4) In the cases of some diseases—of which leprosy is an example—the only fact on which an etiological relationship can be founded is the constant occurrence of an organism with special staining characters associated with a disease. In the case cited, the association is so constant and the characteristics of the organism so special, that there can be little doubt that further investigation will serve to confirm the relationship which is at present strongly suspected.

Conceptions of Infection and Contagion.—Formerly pathologists understood by infective diseases those which are set up by certain poisons, or poisonous substances (whether organised—that is living—or non-organised) either entering the body from without, or manufactured in or by the tissues of diseased individuals. They distinguished between a *contagium* and a *miasma*, the former being an endogenous virus developed in the diseased individual, while the latter was assumed to arise exogenously, that is, outside the diseased organism. According to this view contagious diseases can be transmitted only from man to man, or from animal to man, or conversely; while miasmatic diseases may be acquired without contact with individuals similarly affected. This distinction led to many difficulties.

With the advance of bacteriology these conceptions have become modified. At the present time we include under infective diseases only those which are caused by living pathogenetic germs which enter the tissues from without, and are capable of multiplying in or on the same. We take no account of the differences which exist among these germs in their capacity of living for longer or shorter periods outside the animal body, differences which were the basis of the old distinction between contagion and infection. Infection must be used as the general term, including contagion. It is evident that a disease or lesion called infective may be transmitted by direct contact from the diseased to the healthy, since the germs to which the mischief is due are capable, it may be, of unlimited reproduction within the diseased body; but it does not necessarily follow that it is always, or even usually, thus transmitted. Pneumonia, typhoid fever, and cholera are all infective diseases, but are they ordinarily contagious?

Whether a disease be directly or indirectly contagious, or both, will depend primarily on the nature of the organism which causes the disease. If an infective lesion be due to an organism usually parasitic, then it will be transmitted by direct contact, that is, by immediate transference from living tissue to living tissue. The less parasitic, and therefore the more saprophytic the infective organisms, the greater will be the chances of transmitting the lesion by indirect contact, *e.g.* by the air; for in this

case the organisms can thrive for a considerable time outside the animal body. This is a matter of some practical importance, because a disease the contagion of which is exclusively direct can be stamped out by isolation; while in a disease both directly and indirectly contagious isolation alone is of less avail.

Arranging the more important infective diseases on this principle we find that there are—

i. Diseases caused by organisms *which readily perish outside the living animal body*; these may be directly contagious, and are preventible by isolation, segregation, or destruction of the individual; assisted, of course, by disinfective measures. Examples are syphilis and gonorrhœa. The organisms which cause these diseases are of slight resistance, and outside the animal body soon die.

ii. Diseases caused by organisms of greater resistance, capable of surviving, for a time at any rate, outside the animal body, although incapable of multiplying under such conditions; these, though generally or almost always directly contagious, may occasionally be indirectly contagious also. Examples are variola, scarlatina, measles, glanders, diphtheria. Isolation and segregation with disinfection are usually the best means of preventing infection.

iii. Diseases caused by *organisms capable of thriving outside the animal body*; these are obviously either directly or indirectly contagious; and the greater the saprophytic faculty of the organisms, the greater the chances of indirect contagion. Segregation and isolation are relatively ineffectual as preventive measures; and absolute disinfection is, strictly speaking, the only means of prevention; in practice, however, this is almost always impossible. Examples are tuberculosis, cholera, typhoid fever. It is quite possible that with increased knowledge of the biological conditions of pathogenetic organisms more than one disease at present included in the previous groups will eventually have to be placed in this one. Thus it seems possible that the bacillus of diphtheria may be sometimes a saprophyte.

iv. Diseases caused by *organisms usually saprophytic* but capable of acting as parasites; these are hardly ever directly contagious. Examples are found in tetanus, malignant œdema, and probably in some epidemics of summer diarrhœa. Here also might be included some of the disease conditions originated by the *B. coli*, which is an ordinary inhabitant of the human intestine. The more widely an organism of this class is distributed the less contagious will be the disease caused by it. Tetanus, for instance, is hardly ever directly or indirectly contagious; it is generally acquired independently of any previous case.

Obviously it is a matter of great difficulty to draw a hard-and-fast line between the organisms concerned in the conditions included in the third and fourth groups, and it cannot be said that in every case a definite opinion can be given whether an organism is mainly parasitic or mainly saprophytic in habitat. It must be admitted that here bacteriology cannot as yet always give a complete explanation of the facts observed by

the epidemiologist. The social, racial, local, climatic, and general hygienic conditions are always of great importance in modifying the incidence of infections, and these conditions are no doubt often extremely complex. For instance, a break in direct case-continuity between an epidemic of diphtheria and one occurring in the same area at a subsequent date might indicate for the diphtheria bacillus a mainly saprophytic existence. On the other hand, the existence during diphtheria epidemics of mild cases of sore throat, really diphtheritic in nature, opens up the way for the bacillus being maintained in the human throat and transferred from person to person in a state of slight or suppressed pathogenicity during the period when the disease was apparently non-existent. Such an explanation, however, even if valid in one instance, probably would not account for all such occurrences. Thus the seasonal recurrence so marked in many epidemic diseases, such as plague, constitutes a very difficult problem, which in this particular example is complicated by the possibility that epidemics in man may be associated with epidemics in one of the lower animals, namely, the rat. Indeed, the possibility that in many human diseases there may be an extra-human host, and in some infections an intra-human and extra-human cycle for the morbific agent, has only within recent years been seriously considered. In the non-bacterial infection of malaria the recognition of such an occurrence has to a large extent satisfactorily settled the epidemiology of this disease; and the fact that in yellow fever the interposition of a mosquito is necessary for the maintenance of the disease in an epidemic form has not only furnished a fresh proof for the necessity of keeping the possibility of the recurrence of extra-human hosts in view, but in the disease in question has explained its occasional and local prevalence. Then, again, the biological qualities of an organism must be taken into account. Thus in a bacterium which forms spores no extra-corporeal germination of the spores need take place after they are formed till they again find themselves in the body of an animal. In the case of anthrax, for instance, though there is little doubt that germination often occurs saprophytically, yet in other circumstances the spores can be carried across the world in, for instance, horse-hair, probably without undergoing germination till they pass into an animal's body.

Modes of Entrance of Bacteria into the Body.—It is important to keep such considerations in mind in discussing the ways in which bacteria gain entrance to the body. In the healthy animal the blood and tissues are free from pathogenetic bacteria. Whether all bacteria are absent is a much-disputed point. In the alimentary tract there is an extensive bacterial flora, and the same, though to a less extent, is true of the skin. The pulmonary alveoli and probably the smaller bronchi do not contain bacteria, but probably these are usually present in the larger air-passages. Most of the bacteria in such situations are non-pathogenetic, and are putrefactive organisms living on organic matter either derived from the host or from extraneous sources. Often, however, pathogenetic bacteria are found leading a saprophytic existence on the surfaces of the

animal body. In the intestinal canal of man there are great numbers of the *Bacillus coli*, which is capable of originating suppuration, and is often found in abscesses in connexion with the abdominal organs, more particularly those of the genito-urinary system. Here also there frequently exists the *Streptococcus pyogenes*, one of the most common causes of inflammation and suppuration; in the mouth and on the skin another pyogenetic microbe, the *Staphylococcus pyogenes*, in one or other of its varieties, often occurs. In the mouth there is also often the pneumococcus, which is the cause of acute pneumonic conditions, and may originate other inflammations also. Why these bacteria pass from their usual harmless existence to a pathogenetic state is a question for future consideration. When a healthy individual comes in contact with one suffering from bacterial disease, the opportunity for becoming the host of pathogenetic bacteria of less universal distribution arises; and while not suffering from disease himself, he may yet be the carrier of infection to others. Formerly this factor was no doubt often the cause of the outbreaks of erysipelas in hospital wards.

We shall now consider how bacteria brought to the body gain a footing in or upon it. A frequent means of entrance is through some wound, and it is possible that infection may occur in this way even in the alimentary tract, where not only may an injury be caused by the ingestion of hard material in the food, but where the irritation of small inspissated particles, especially if long in contact with one part, may originate an abrasion; though it is fair to say that post-mortem evidence of such an occurrence is not very frequently obtained. Sometimes a morbid condition of a surface of the body, due to non-microbic causes, may enable infection to take place. A familiar example is found in the suppuration which may occur in glands related to a part of the body where the epithelial catarrh found in eczema has denuded the cutis vera of its covering. The entrance of bacteria into the body is frequently secondary to effects produced by them on the cells of the internal or external surfaces of the body. In such a case the superficial cells may die, and thus lose their intimate connexions with each other and with the underlying tissues; so that bacteria may gain access to the subjacent structures by direct growth, or, mechanically, through the movements to which all parts of the body are subject during ordinary active life. A probable example of this is frequently seen in the skin infection which takes place through hair-follicles or sebaceous glands, and in some of the tonsillar infections. In this case the tonsillar crypts, which are so often attacked, present little more than a single layer of flattened cells covering the subjacent lymphoid tissue. The local activity of bacteria in such a case may include not only the death of superficial cells, but also the origination of a proliferative catarrhal process. The consequent denudation is no doubt often a factor in such infections as those which are seen in the lung. Another method by which bacteria may gain entrance to the body is by being taken up into the tissues by means of the wandering cells often found on internal surfaces, especially those of the lungs

(Stohr (320), Durham (95)). The activity of these cells can be seen in practically every lung, in which the fine pigment inhaled as smoke is taken up and finally deposited in its interlobular spaces and lymphatic glands. It is unnecessary here to go into the question of the origin of these cells; suffice it to say that they can be frequently seen in the lymphatics carrying the pigment in their protoplasm. That such cells may take up bacteria attached to dust particles there is no doubt, and the occurrence may explain some of the cases where a tuberculous infection of the bronchial glands occurs without any apparent source of infection. A similar explanation probably accounts for certain cases in which bacteria, of which the tubercle bacillus may be again taken as a type, gain entrance through the walls of the alimentary canal.

Conditions in the Infecting Agent modifying Pathogenetic Action.—The mere introduction of pathogenetic germs into the animal body is not in itself sufficient under all conditions to cause disease. What will happen depends on many factors which are partly connected with the infecting bacterium, partly with the infected organism. From the side of the bacteria the following are the most important.

(*a*) *Number of Bacteria Introduced.*—Some organisms will produce disease when they have been introduced into the body in very small numbers. Others are virulent only when received in large numbers. Thus guinea-pigs succumb to the smallest injection of the tetanus bacillus, and rabbits generally acquire a fatal septicæmia when injected with a very small number of virulent pneumococci. On the other hand, a large number of the *Bacillus pyocyaneus* is required to bring about a fatal septicæmia in rodents, or of pyogenetic staphylococci to produce suppuration. To some extent, no doubt, these laboratory observations apply also to natural conditions, especially since experiment shews that the result produced often varies with the quantity of germs introduced. Thus a small number of the *Bacillus pyocyaneus* will lead to a small local abscess only, a larger number will lead to local necrosis, and a still larger number to septicæmia and death. If we exclude the rare cases where a single bacterium may give rise to a fatal infection, we find generally that an animal can dispose of a certain number of an organism to which it is susceptible without manifesting signs of disease.

The bearing of these observations on the phenomena of natural infection is obvious. It finds practical recognition in the hygienic principle that in many infectious diseases the greater the air-space round an infected individual the less the risk of infection to persons in the same room. No doubt other factors besides the concentration of virus contribute to this result, but such concentration must be taken into account.

The abundance of germs leaving the affected individual favours indirect contagion by causing a wider diffusion, and by offering more chances of ectanthropic infection. In some infective diseases, as for instance in tetanus, the organisms are discharged from the body in small numbers; in others the numbers discharged are great, especially in diseases which affect the excretory passages, or organs in direct or easy

communication with such passages. In bacterial intestinal lesions,—for example, in enteric fever and cholera—thousands of bacilli or vibrios must pass away with the dejecta: similarly in pulmonary infections, such as tuberculosis, pneumonia, influenza, the sputa swarm with bacteria, and minute portions of expectoration discharged into the air may carry the organisms to a considerable distance. From extensive ulcerating bacterial skin affections—as, for example, in nodular leprosy—myriads of bacilli may be discharged. The urine, again, may contain numerous organisms—as in gonorrhœa, some forms of puerperal fever, enteric fever, and genito-urinary tuberculosis. When the bacteria are relatively incapable of saprophytic existence, or when from the nature of the disease the discharges can be closely guarded, the danger of increased diffusion is so far limited. Thus the urine in gonorrhœa and the sputum in acute pneumonia are not dangerous sources of infection. On the other hand, consumptives by their expectoration contribute largely to the wide diffusion of the tubercle bacillus; from the chronic nature of their disease they are less easily controlled, and are reckless with their expectoration, though within recent years great improvement has taken place in this respect. It will thus be seen that the risk of infection due to mere numbers of bacteria varies greatly in different diseases.

(*b*) *Virulence.*—As the shape and forms of bacteria may vary or may be altered by changes in their surroundings, so likewise may their physiological, chemical, or vital activity be greatly modified—often to such an extent that in many cases we seem to come very near new species. Among pathogenetic bacteria loss of virulence is not only the most important change, but also that most frequently observed. Thus the pneumococcus, if continuously grown on ordinary media, very soon ceases to be virulent, and this loss of virulence is permanent; similarly the diphtheria bacillus on agar-agar may become less virulent. This loss of virulence is called *attenuation*, and besides prolonged cultivation in or on artificial media, it may be brought about in many ways, as by heat, evaporation, drying, or the addition of chemical substances to the culture media: these methods, however, require no further consideration. Attenuation may be temporary or it may be permanent, as in the case of anthrax, where the loss of virulence may be, moreover, accompanied by loss of spore-formation. It is often found also that an organism obtained from a bacterial lesion of severe or malignant type soon loses its virulence, or is from the outset less virulent than an organism separated from a less severe case of the same lesion. The streptococci are in this respect, perhaps, the most variable of all germs. This variability in virulence cannot be satisfactorily explained at present; but it must necessarily lead us to be cautious in our attempts to interpret vital phenomena by means of test-tube reactions only.

The virulence of many organisms may also be permanently or temporarily increased, either by changing the composition of the nutrient media in or on which they grow, or—especially if the animals be relatively insusceptible—by passing the organisms through a series

of animals (a process which is called "*passage*"). In some cases, however, continued passage will lead to permanent attenuation—an important observation in so far as it helps to throw light on the natural decline of many epidemics, which may cease by virtue of a gradual attenuation brought about by continuous transmission from man to man. Sometimes when by passage the virulence of an organism is increased for one species of animal it is diminished for another. Thus, when anthrax is passed through a series of guinea-pigs, it becomes more virulent for the guinea-pig and less virulent for the ox.

Most writers assume the existence of natural non-virulent varieties in the cases of the organisms of cholera, typhoid, diphtheria, pneumonia, and traumatic infections. Thus the pneumococcus has been found for long periods inhabiting the mouths of apparently healthy individuals. Under special conditions—unknown to us—such harmless varieties may acquire virulence either before or on gaining access to the body, and will then be capable of producing the lesion proper to each. This is possible, if not probable: it is safer, however, to suspend our judgment for the present.

(*c*) *The path of infection* is of some importance in modifying the course of infection. In experimental work the same number of bacteria will, generally speaking, cause a greater effect if introduced into the animal body either intravenously or intra-peritoneally than if injected subcutaneously. Thus, when some of the pyogenetic organisms are introduced under the skin, a local abscess only results, while if they be injected intravenously rapid death with widespread distribution of the bacteria all over the body may ensue. In certain cases, however, when intravenous injection is practised the bacteria are met in the blood by conditions fatal to their vitality in a way that does not happen when they are lodged under the skin. Facts similar to those derived from animal experiment occur in natural infection in man. Here the susceptibility to bacterial infection of such tissues as the peritoneal membrane and the synovia of joints, as compared with the subcutaneous tissues, is well known to the surgeon.

(*d*) *The interaction of various organisms* probably is occasionally of importance. In many infective processes we often find two or more organisms present, that is, we have concurrent infections by several organisms. Thus in many abscesses the *Staphylococcus pyogenes* and the *Streptococcus pyogenes* are both present. The result may be a summation of effect or a preparation by one organism for the growth of another. It has been shown experimentally that a non-pathogenetic organism (that is, an organism which does not possess the power of producing specific or non-specific morbid changes when placed in the tissues) may be rendered deadly when another organism is introduced at the same time. We also know that the virulence of many pathogenetic organisms is often increased or decreased by the concurrent inoculation of another organism, which again may be non-pathogenetic: thus it was shown by Sanarelli (303) that the injection of dead cultures of *B. coli*

increased the pathogenetic effect of the *B. typhosus*, and Vaillard (333) has shown that the pathogenicity of the tetanus bacillus is much increased if the *Staphylococcus pyogenes aureus* be also present. This interaction of micro-organisms has not as yet been sufficiently investigated, and here this brief allusion must suffice; it has been studied by Dr. Klein (156), to whose paper the reader is referred. In this connexion an important point is that if in certain lesions the same collection of organisms be constantly found, we may be led astray if we fix on one of them as specific, and neglect the others as contaminations. A study of the correlation and interaction between the various organisms frequently or almost invariably found together, may in future explain many clinical phenomena and observations as yet obscure.

Conditions in the infected Animal modifying Pathogenetic Action.—Susceptibility to a disease is often denominated predisposition; it may be either natural or acquired. A natural predisposition may be either a property of a species, which as such is transmitted from parent to offspring (racial predisposition); or it may be an accidental character of one or more individuals of a species (individual predisposition), not necessarily transmitted to the offspring. Thus guinea-pigs are naturally extremely susceptible to tuberculosis; man to syphilis and diphtheria. On the other hand, man is insusceptible to foot-and-mouth disease, the common fowl to natural infection with tetanus. In many cases resistance is relative and partial only, as, for example, in the case of man's resistance against tuberculosis, leprosy, anthrax, or cholera. We must thus assume that sometimes predisposition is entirely or partly absent. The cause of individual predisposition we do not understand.

Predisposition probably depends on various factors, among which the most important may be—(1) intrinsic cell properties; and (2) extrinsic conditions reacting harmfully on the body and its tissue-processes. Within certain limits an organism has special cellular mechanisms which may ward off an infection. Thus the acidity of the gastric juice, and a proper supply of it, may prove too strong for the cholera vibrio; the ciliated epithelium, the sensitiveness of the bronchial mucous membrane and the germicidal action of the mucus may protect the respiratory organs against an invasion by tubercle bacilli. Again, we know from Löffler's experiments that the age and nature of the epithelial lining are conditions of great importance in the case of diphtheria: the vaginal mucous membrane of young animals is easily attacked, but that of old animals is very resistant. Orth and Wyssokowitsch have shewn that traumatic lesions at a seat of infection will cause a local predisposition to certain infective processes. These investigators produced a well-marked malignant endocarditis by first causing a slight injury to the cardiac valves, and then injecting a culture of staphylococci: when the valves were intact endocarditis did not result. In natural infections in man we have an example of the origination of such personal dispositions in the occurrence of pulmonary tuberculosis in miners exposed to the inhalation of granite dust (*see* Haldane, Martin, and Thomas (143)).

I. *Acquired Predisposition.*—Various means exist by which a refractory or resistant animal can be rendered susceptible. We may reduce the natural resistance of an animal against a microbe either by general or special interferences, and thus establish an acquired disposition. The former are of more interest to us, as they prove how much good can be effected by sanitary surroundings in the prevention of disease.

General Interferences.—1. Canalis and Morpurgo (67) have shewn that by means of *starvation* we can render pigeons, which are naturally resistant against anthrax, extremely susceptible to this infection. They succumb, either if we allow them to starve immediately after the inoculation, or starve them six days previously and then inoculate them, at the same time continuing the process of starvation. But if we feed them regularly immediately after inoculation, then, in spite of having previously been starved for six days, they will survive.

Similarly hens, naturally immune, become susceptible to an anthrax infection through starvation; rats, on the other hand, do not lose their natural immunity in this manner. Sacchi (296), by means of starvation, succeeded in rendering a local anthrax infection in pigeons a general infection. Pernice and Alessi (268) proved that dogs, hens, pigeons, and frogs can be rendered susceptible to anthrax by depriving them of water.

2. Again, *fatigue and loss of blood* are capable of removing the natural immunity of animals. Thus Charrin and Roger (71, 290) have shewn that the normal white rat, which, as is well known, is very insusceptible to anthrax, becomes susceptible to this disease in a marked degree if it be made to work a treadmill in a cage until it is thoroughly fatigued. Rodet and others have established an acquired disposition by inducing a general anæmia by artificial loss of blood.

3. *An unsuitable diet*, as Dr. Hankin has shewn, may remove the resistance of the body against anthrax. Thus refractory rats, fed on sour milk and bread, lose their insusceptibility; a pure meat diet enhances it. Hans Leo (182) administered phloridzin in small doses with the food for some days previous to inoculation, with the result that sugar shewed itself in the tissues of the animal under experiment: this animal now became highly susceptible to a glanders infection, which in its normal condition it was able to resist. The same treatment, however, did not increase the susceptibility of rats to anthrax and tuberculosis.

4. *Exposure to heat, cold, and moisture* has been investigated by Pasteur, Petruschky, Fermi and Salsano (119*a*), and others. Thus on immersing a hen in water it loses its resistance to anthrax, and the same occurs on reducing its temperature by the administration of antipyrin. Frogs, if kept at a temperature of 25°-35° C., will succumb to anthrax. Guinea-pigs and white mice, which are resistant to avian tuberculosis, can be rendered susceptible by keeping them after inoculation in a warm chamber at 33°-35° C.

We see, then, that it is easy by such general means as starvation, fatigue, exposure, and bad diet to reduce the insusceptibility of certain

animals to infective diseases. Now, if in a community of which the normal individuals are insusceptible, a certain number of these, through one or other of the above causes, becomes susceptible, then, for these modified persons, the disease may be extremely contagious, though non-contagious for the community as a group. In such a case we must inquire by what processes a disease has become contagious for a certain community, and while preventing by disinfection and other appropriate measures a further distribution of the contagium, we must so improve the social and personal hygiene as to undo the tendency to modification.

A consideration of tuberculosis from this point of view will make our meaning clearer. We cannot hope to destroy the *contagium vivum*, it is too widely distributed; nor can we destroy the affected individuals —such a process would be unavailing, even if free from other objections. How, then, can we prevent the spread of the disease? If, as it seems, the disposition to it be due to any or all of the above causes, let these be removed. Now we know that a healthy man is relatively immune to tuberculosis; we know also that bad hygiene, exposure, and the like, may render him susceptible to it; the rational preventive measure, therefore, is to counteract the causes of this acquired susceptibility, while at the same time we order all consumptives to destroy their sputum. Whether the effects of such measures might not be advanced by a compulsory segregation of patients, at any rate of those in the last stages of disease, is a question for serious consideration. That improved personal hygiene and public sanitation and a higher standard of life materially diminish the death-rate from consumption is already ascertained; the vital statistics of England clearly demonstrate that sanitary legislation has coincided with a considerable diminution of the number of deaths from pulmonary tuberculosis (*vide* Vol. I. p. 49).

Such considerations will serve to explain the meaning and nature of *endemicity*, or the state, both of the individuals living in a district, and of the medium in which they live, which favours a certain infective disease. Undoubtedly cholera is a disease for which, if it appears sporadically, a special individual bent is required; and if it appears in epidemics, there must be the local predisposition in addition. Now in certain parts of India, as, for example, Lower Bengal and Assam, cholera is always present or "endemic." Such endemic areas are, for the most part, over-populated, poor, or extremely unhealthy. These and similar factors may reduce the resistance of the population, and render the existence of the evil a necessary consequence.

We should remember, however, that, in contradistinction to individual disposition which applies to certain individuals of a species, there is also a *racial disposition* which applies to all members of a species. Negroes are seldom affected by yellow fever, and the same is true of the mulatto. There are numerous examples of such phenomena in the laboratory. Thus, of dogs which are relatively resistant to anthrax, black dogs are less so than white ones. Black and grey rats are less susceptible to anthrax than white rats. Field-mice, again, are extremely

susceptible to mammalian tuberculosis, while white mice are practically immune.

Again, *age* is a disposing factor, for young individuals acquire certain affections—for example, enteric fever—more easily than adults; this rule also is amply borne out by animal experiments. Oemler (263) has shewn that young pigeons are much less refractory to anthrax than old ones. On the other hand, among mammals, sucklings appear to be less liable to some infective fevers, such as measles and scarlet fever, than to others.

Special Interferences.—1. It was once thought by Tizzoni and Cattani (325) that it is impossible to render rabbits immune to tetanus after the *removal of their spleens*, and that the removal of the spleen will destroy the natural immunity of dogs to tetanus and anthrax. That, however, the acquired disposition does not in all cases depend on the removal of the spleen is shewn by the experiments of Foà and Scabia (125) and others, who worked with the diplococcus of pneumonia and the *B. pyocyaneus*, and proved that, for these infections at least and the immunity towards them, the spleen is of no importance; for if we allow the animal to recover its weight and strength completely, its immunity will persist. The temporary loss of resistance is probably explained by other organs of the hæmolymph system taking on vicariously the functions of the spleen. According to Canalis and Morpurgo (67), pigeons are rendered less resistant to anthrax by *removal of the pancreas.* This operation also predisposes animals to septic infections; and, according to Sawtschenko, the same happens after section of the spinal cord in pigeons. Roger (291) has brought forward evidence to shew that the removal of the great omentum lowers the resistance of animals to pyogenetic infection.

2. Again, there are many experiments to prove that bacteria, absolutely or relatively harmless to animals when injected in pure cultures by themselves, *become intensely virulent when at the same time we inject certain chemical bodies* at the seat of lesion. Thus Vaillard and Rouget (333) have shewn that in animals immune to tetanus a characteristic infection can be brought about by injecting lactic acid or trimethylamine with the tetanus bacillus. Bujwid (55) found, on antecedent injection of sugar solution into the subcutaneous tissue of animals, that an inoculation of the *Staphylococcus pyogenes aureus* was in most instances followed by marked suppuration,—a result not easily achieved by means of the staphylococcus in the absence of previous sugar injection. Lastly, hypodermic injections of dextrose and lactic acid will render guinea-pigs and white mice susceptible to avian tuberculosis, and white mice also to mammalian tuberculosis. This was shewn by Fermi and Salsano (119*a*), and it is important to note that avian tubercle bacilli, repeatedly inoculated into guinea-pigs, rendered susceptible by such injections, become virulent for normal guinea-pigs. Here we may also mention Drs. Klein and Coxwell's (157) experiments, which shew that in frogs and rats the natural immunity to anthrax may be destroyed by means of a chloroform-ether narcosis.

3 Then, again, the metabolic *products of certain, it may be harmless,*

micro-organisms are often capable of rendering a non-pathogenetic germ pathogenetic. We have already referred to this point. Examples are mentioned by Roger (290), who has shewn that rabbits will succumb to quarter-evil if, simultaneously with the bacilli, the chemical products of the *Bacillus prodigiosus*, *Proteus vulgaris*, or staphylococcus be administered. Dr. Klein (156) and others have given further proof of this. Other allied bodies—vegetable ferments, for instance—have the same effect.

Very little progress has been made within recent years in the further elucidation of the conditions modifying disposition (cf. Lubarsch (190)). We cannot as yet formulate any hypothesis as to the mechanism by which an increased disposition to disease operates. We shall, however, revert to this point later.

II. *Hereditary Predisposition.*—Like other characteristics a tendency to disease can be transmitted from parent to offspring. The part played by inherited tendency as compared with the part played by actual transmission of the infective agent from parent to child has given rise to discussion. Thus, tuberculosis is a disease of extra-uterine life, but undoubtedly cases of congenital tuberculosis do occur, as shewn by Merkel, Landouzy, Rindfleisch, Birch-Hirschfeld, and others; and much more frequently than congenital tuberculosis do we find tuberculosis in infants and children during the first months or years of life, as shewn by Queyrat, Landouzy, Müller, and others. It is almost universally believed that the undisputed hereditary succession of tuberculous processes depends, not on a direct transmission of the elements of the disease from parent to offspring, but on an hereditary transmission of a proclivity. Baumgarten (15), however, believed that the heredity of pulmonary tuberculosis depends on an intra-uterine or congenital infection of the fœtus with tubercle bacilli from the mother, and he supports these views with the following arguments. Besides the existence of congenital tuberculosis, Birch-Hirschfeld and others have demonstrated that in man, as well as in animals, tuberculous infection through the placental circulation is not only possible but does actually occur. Observations and experiments on animals shew: (*a*) that congenital tuberculosis in the larger susceptible mammals is not very rare (Johne); (*b*) that of the offspring of tuberculous guinea-pigs twenty-five per cent are born with congenital tuberculosis (de Renzi); (*c*) that intra-uterine tuberculous infection is possible in rabbits and mice (Gärtner (131)); (*d*) that chickens hatched from eggs inoculated with tubercle bacilli manifest tuberculosis, and the eggs of canaries inoculated intra-abdominally with tubercle bacilli are frequently infected (Maffucci (201), Baumgarten and Gärtner). From analogy, therefore, Baumgarten assumed that in man also the tubercle bacilli are transmitted congenitally *in utero*, and that if the disease be not apparent at the time of birth the bacilli remain dormant in the tissues (of the liver, for instance), causing at first only small, obscure foci, and being for some time impaired in their development. Possibly tubercle bacilli may thus be stored up in the tissues

of the fœtus. But how is it that such offspring often, or indeed generally, do not manifest the disease proper until years afterwards? The answer must be because their tissues are sufficiently resistant to keep the activity of the bacilli in abeyance, or in some cases sufficiently strong even to destroy them altogether. But if later they lose this resistance, the bacilli are then placed in the conditions required for successful activity. We are thus led again to assume a proclivity in the cases under discussion. And is it not possible that the appearance of this proclivity is favoured by certain tendencies transmitted by inheritance? Hereditary peculiarities are often limited to a definite period or age; and we find that in the offspring the disease often shews itself at about the same age as it did in the parent—a point of importance in a philosophical consideration of hereditary transmission.

Animal experiments cannot prove much in investigations of this nature, for in questions of hereditary transmission we must consider each species by itself. Guinea-pigs, rabbits, mice, and hens—the animals generally employed—are naturally highly susceptible to tuberculosis, and hence the predisposition is an inherent property of the parent, and therefore also of the ovum or embryo. As the tissues of the normal parent offer no resistance, we cannot possibly expect those of the offspring to do so. Animal experiments do, however, make it certain that by no means all the offspring of tuberculous animals harbour latent bacilli in their tissues, and we have no right to assume that such a condition of things commonly exists in man. For the present we must assume that in most cases the offspring of tuberculous parents inherit only the proclivity, and subsequently become infected from without. Hence the so-called "heredity" of pulmonary tuberculosis finds its explanation in the following possibilities:—(1) Congenital infection, either germinal from the male (of this there is no evidence), or placental, followed by immediate results; (2) Congenital infection with inherited disposition, followed, after a period of latency, by recrudescence at a subsequent date; (3) Inherited disposition with infection at a later date. Now since in the case of tuberculosis we find some of the characteristic features of heredity—for instance that atavism is not uncommon, and that the hereditary tendency is often limited to one sex and to a definite age—and since it requires great faith to believe in a bacterial sleep lasting through many years as a complete explanation, we must incline to Virchow's doctrine of the existence and influence of an inherited predisposition to tuberculosis, even though our modern conception of predisposition differs from his.

The inherited disposition may be either specific or non-specific. The parental disposition may have been due to many agents and factors; and it is possible that some of these, although not of the same nature as the resulting tuberculosis, have been the cause of the congenital bent transmitted to the offspring. This evidently could not be an inherited specific predisposition; that is, it is quite possible that a non-tuberculous condition of a parent may lead in a child to an inherited predisposition

favourable to the development of tuberculosis. A predisposition can only be specifically inherited in cases in which the child was born of tuberculous parents or ancestors. A child born of a parent who becomes phthisical some years after its birth cannot with certainty be supposed to have inherited a specific tuberculous proclivity. The eventual acquirement of the disease by the parent cannot make the inherited proclivity any more specific; it can prove only that certain conditions and abnormalities of the parent which eventually favoured tuberculosis have been transmitted to the offspring.

Although tubercle and also leprosy bacilli have been found occasionally in the testes and ovaries, and even in the seminal fluid of diseased individuals, there is no evidence whatever that germinal infection ever does occur: in fact Gärtner has shewn that in animals, even if numerous tubercle bacilli are contained in the seminal fluid, it is the mother which is first infected, and not the ovum or embryo. The like is true of all infective diseases with the bacteriology of which we are acquainted; and for such of them as appear congenitally, infection must practically always take place through the placental circulation. This is exactly what occurs in animals in which it can be demonstrated more readily. Placental infection in animals has been conclusively shewn to occur in congenital anthrax, chicken-cholera, suppurative lesions, and tuberculosis: in man it is found in pneumococcus and suppurative infections, in typhoid fever, anthrax, relapsing fever, and tuberculosis; and is assumed to exist in measles, scarlatina, and small-pox, diseases the etiology of which is still obscure. Where placental infection occurs, the micro-organisms are taken up chiefly by the fœtal liver; there, according to Maffucci, a keen struggle for supremacy occurs, the embryonic gland as much as the adult one being possessed of marked defensive capacity. If the bacteria prove victorious, then the fœtus may present the characteristic lesions produced by the infection—as, for instance, in many cases of tuberculosis, septicæmia, or pyæmia; or it may present them in a modified form, which after birth may assume the ordinary appearance, the embryo being, as already explained, apparently endowed in these cases with a more or less marked resistance. For instance, although anthrax bacilli, typhoid bacilli, and pneumococci may pass through the placental circulation, yet, as Prof. Welch says, "no instance has been observed in the fœtus of fully developed anthrax, of croupous pneumonia, or of intestinal lesions by the typhoid bacillus, although in several recorded instances these bacteria have unquestionably invaded the fœtus from the mother. The characteristic lesions have, however, been found so soon after birth as to indicate positively congenital infection." It is still a debated point whether the healthy placenta will allow pathogenetic organisms to pass into the fœtal circulation; some writers assume that a lesion, such as a hæmorrhage for instance, is necessary. It seems, however, that the factor is rather one of the time or duration of infection and of the virulence of the pathogenetic organisms. The lesson which we derive from these various

experiments and observations on the fœtal infections is one of caution in the use of the term heredity in respect of infective diseases; a strict terminology is, if possible, the more necessary now that Weissmann's hypotheses have so great an ascendency.

A. A. Kanthack, 1896.
James Ritchie, 1906.

II. Changes produced by Bacteria in the Animal Body

A. Tissue Changes

We now turn to consider in a general way the tissue-changes which can be observed in connexion with infective disease. These may be local or general, or local and general, according to the kind of bacterial action with which we are dealing. To look first of all at the local manifestations.

These may be grouped under two headings, first, degenerative changes which may or may not end in death; secondly, reactive changes the feature of which is an exhibition of cellular activity.

Local Changes—(*a*) *Degenerative and Necrotic.*—These to a certain extent vary with the tissue attacked, but include practically all the known forms of cellular degeneration. In the case of connective tissues, the cells may sometimes die without any great change in their form or in the form of the nucleus, and such cells in a section can frequently be recognised as dead simply because the nucleus has lost its capacity of reacting to basophilic stains and has become oxyphilic, while the protoplasm has become granular. Changes of this kind were supposed by Weigert to be of the nature of an intracellular coagulation, and were termed a "coagulation-necrosis." Sometimes this cellular change may be accompanied by a coagulation of the albuminous fluids present around the cells of the part, either naturally or as the result of a process of exudation. In such cases it is probable that the death of the cell has been rapid, and has not been preceded by any prolonged period of interruption of the cellular metabolism. Sometimes there is evidence of some such period during which the changes in metabolism have had time to have a more pronounced effect on structure. This may be evidenced in various ways. The nucleus of a cell, for instance, may lie broken up into fragments in the cellular protoplasm—the condition to which the term "karyorrhexis" is applied—or the protoplasm may present variations from its normal appearance. It may simply shew differences in staining reaction, a common appearance being one in which a cell with ordinarily oxyphilic protoplasm exhibits an imperfect basophilic tendency. Frequently there are structural alterations such as vacuolation, unwonted granulation, and, it may be, breaking up of the cytoplasm with actual loss of cellular outline, and evidence of fatty degeneration may also be manifest, especially in the long-standing or chronic infections. In very

acute local infections the centre of activity may very soon after the commencement of the change consist simply of an agglomeration of cellular débris, while in chronic infections—for example, in tuberculosis—the central part of a lesion may chiefly contain the products of fatty degeneration; to this latter event the term caseation is applied. In chronic infections other degenerations—hyaline, mucoid, and so forth—occur.

The walls of small vessels are, especially in acute conditions, frequently affected, and the occurrence of minute hæmorrhages (ecchymoses) may be observed. A less serious interference with the vitality of the cells lining the blood-vessels is undoubtedly a factor in the occurrence of the œdema which is frequently seen round a focus of infection. This œdema may be widespread and may affect a large part of the body, the involvement of a whole limb being very frequent in infection by some of the pyogenetic organisms, by the streptococcus of erysipelas, by the *Bacillus anthracis*, and by the bacillus of malignant œdema. The development of œdema may be associated with a correspondingly wide distribution of the causal bacteria, or may occur when the bacteria are confined to the immediate neighbourhood of the infected spot, as in many cases of anthrax in man. The œdematous fluid infiltrates all the tissues of a part, but is, of course, particularly well marked in those of loose texture. When the skin is involved the occurrence of large or small blebs is not uncommon, and into them small hæmorrhages from the subjacent papillary vessels may take place. Sometimes the course of an infection may be cut short by the effects of œdema causing the death of the affected individual. This not infrequently occurs in bacterial infections about the neck, in the septic conditions sometimes called Angina Ludovici, in malignant œdema, and in anthrax where death from asphyxia is not uncommon. In intracranial infections, especially those of the meninges, such as tuberculous meningitis, the œdema set up either by direct effects on the vessels, or indirectly by mechanical interferences with the normal secretion or absorption of the cerebrospinal fluid or cerebral lymph-systems, may have serious effects on cerebral function and be a very potent factor in the occurrence of death. In the more chronic infections, such as syphilis, cellular degenerations (*e.g.* hyaline degeneration) are often observed in the small vessels, and these by narrowing the lumen contribute to the lack of cellular nutrition occurring in the focus of infection.

The distribution of degeneration and death of cells in connexion with a focus of infection varies greatly in different cases. In some, as in local pyogenetic infections, it is small, and it may be that it is irregular, that is, cells which are degenerated or dead may lie in close contact with others either unaffected or shewing signs of stimulation to increased vital activity in connexion with the infection. This may occur even in acute conditions, but is most marked where the bacteria are comparatively slow in their action. Thus the evidences of cellular degeneration and cellular reaction are often present side by side, or actually intermingled

the one with the other. This is often well seen in slow infections of bones, such as occur in the caries caused by the action of the tubercle bacillus, where there is a slow crumbling away of minute particles of the tissue. Not infrequently, however, especially in acute cases, comparatively large areas of tissue undergo death almost simultaneously in all their component parts. A common example is found in a boil, and still more so in a carbuncle; in these conditions which are traceable to the pyogenetic cocci, large areas of subcutaneous tissue die as the result of direct bacterial action—without much or any previous degeneration—and to the naked eye assume a greyish and bloodless appearance ("sloughs"). A similar process is responsible for the necrosis of the Peyer's patches in typhoid fever. Sometimes in an infection there occurs a condition of moist gangrene, it may be of a limb or part of a limb, it may be of a portion of the trunk, for example, of the scrotum, or of the face as in noma. This may be secondary to direct bacterial action, and be due to the cutting off of the blood-supply to a part, by the pressure of exudation on blood-vessels or in consequence of the thrombosis which frequently follows on the injury of the walls of vessels in an area where bacterial activity is going on; the tissues as a consequence die, and the changes which subsequently occur are usually attributed to the secondary action of the putrefactive bacteria constantly present on the surfaces of the body. In other cases an excessive production of poisons by a bacterium may cause gangrene when the occurrence would not, in ordinary circumstances, be looked for, *e.g.* in some streptococcal infections when local death appears as a complication. On the other hand, while the action of certain bacteria, such as the *Bacillus œdematis maligni*, when investigated experimentally, often results in gangrene, in the case of many bacteria isolated from various gangrenous conditions, though grave effects may supervene on animal inoculation, gangrene is not caused. Thus, the occurrence of gangrene during an infection may depend on a pre-existing weak vitality of the tissues. This is borne out by such facts as the frequency of noma in ill-fed children who are recovering from some exanthem, and also by the phenomena of diabetic gangrene in which a trivial infection often acts as a starting-point for widespread tissue-death. Supplementary evidence is also furnished by the fact that an ordinary *Staphylococcus aureus* has been found to cause gangrene in animals suffering from glycosuria. Similar principles are probably also concerned in the occurrence of pulmonary gangrene, though here there are two views: in the first place, that gangrene may follow pneumonia and be caused by the pneumococcus, especially if external conditions affecting the vitality of the lung-tissue be present: secondly, that gangrene follows pneumonia, but is caused by secondary infection with other organisms.

In certain infections of bone considerable masses of osseous tissue may perish. This may either be due to direct bacterial action on the bone-cells or may be secondary to interference with the blood-supply, as for example by the detachment of the periosteum due to exudation

between it and the bone, or to thrombosis of the vessels in the Haversian canals.

(*b*) *Reactive Changes.*—By far the more important of the local effects of bacterial action are those which indicate not degeneration or death but increased activity on the part of cells. Such increased activity is what is essentially involved in what is called the reaction of the body against infection. The most important local manifestations of cellular activity observed during infection are, first, the increased activity in the amœboid cells of the body, and the local proliferation of the fixed tissue-cells. The group of changes by which such increased activities are manifested constitutes an essential part of the process of inflammation. In fact, inflammation, whether in man or in animals, is in the vast majority of instances caused by bacterial action. [*Vide* "Inflammation," Vol. I. p. 723.] From the general standpoint of infection the incidents of the process which concern us are (*a*) the leucocytic exudation; (*b*) the proliferation of certain fixed cells of the affected part. With the vascular changes we have little to do; their interest to us lies in the development of the fluid exudation which follows and constitutes the œdema already referred to. It may be pointed out that no chemical analysis of the œdematous fluid can help us towards an appreciation of the points regarding it which, from the standpoint of infection, are probably the most important. In the leucocytic exudation we have the most important of the reactive phenomena. While the occurrence of such exudation in all inflammations, however caused, shews that many kinds of stimuli may influence leucocytic movement and many different effects may result from leucocytic emigration, there are no inflammations in which the significance of the event is greater than in those of bacterial origin. In other inflammations the chemiotactic influences which attract the leucocytes from the vessels may be consequent on the changes produced in the fluids of the surrounding parts by the presence of the inorganic chemical irritants causing the inflammation, or by the changes produced in the constitution of these fluids from the presence of dying or dead tissue-cells, and the chief effects may be the removal by phagocytic action of the irritants and of their products. In inflammations of bacterial origin such factors may also be involved, but here there is added the stimulation produced by emanations proceeding directly from the protoplasm of the invading bacteria, and the main effect may be the death of the bacteria and the digestion of the bacterial cells. How complicated the action of the factors involved in the process may be will be shewn in the section on Immunity. Very important also, in bacterial inflammations, is the other incident of the inflammatory process, namely, the proliferation of the fixed cells of the affected part. From the standpoint of infection one aspect of this is especially noteworthy. Many of the cells produced by the proliferation may take part in the same series of effects as those produced by cells derived from the blood. Often both in acute inflammations, as, for instance, in those occurring in the peritoneum, and in chronic inflamma-

tions, such as occur in tuberculosis and leprosy, either the actual pre-existing tissue-cells or—undoubtedly more often—the cells resulting from the proliferation of these may be observed to contain the invading bacteria in their protoplasm. Nor is this phagocytic action confined to the inception of bacteria; frequently cells derived from the tissues, as, for instance, cells derived from proliferation of the endothelial lining of pulmonary alveoli in pneumonic conditions, may take up and digest red blood-corpuscles which, in consequence of the fragility of capillaries, have been shed into an inflamed area. Further, cells derived from serous membranes or from ordinary connective-tissue cells may be seen to contain in their protoplasm polymorphonuclear leucocytes from the blood, whose previous phagocytic activity is shewn by the presence in their protoplasm of the bodies of the bacteria which caused the whole sequence of events. The meaning of this double phagocytosis—the taking up of the cells which themselves have taken up bacteria—is by no means clear. Such intracellular destruction of leucocytes may really be merely an extension of the normal process by which these cells are destroyed when their life-cycle is ended; the phenomenon is well worthy of further investigation. We cannot, however, limit the function of the fixed tissue-cells which take an active part in inflammation to phagocytosis. It is quite possible that by their secretions they play an important part in modifying the composition of the surrounding lymph, and thus produce substances concerned in the complicated process by which bacteria in the tissues are killed. With the other great effect of the proliferation of fixed tissue-cells, namely, the formation of fibrous tissue, which so often is the expression of the injury done by the bacteria to the progenitors of the fibroblasts, we are not concerned here. In connexion with the leucocytic exudation in bacterial inflammations and with the reaction of the cells of the infected tissue, it may be pointed out that during the further development of the infection many examples of the reactive types of cells may die. This accounts for the abscess-formation which so often occurs during the course of bacterial activity in the body and for the death of the newly formed cells seen in the infective granulomas. The death of these cells may be preceded by the same degenerative changes as those described in the ordinary cells of a part during infection.

The foregoing statement briefly summarises the pathological changes produced in any one part of the body when the normal inter-relations and inter-dependences of the cells are interfered with by an invasion of foreign living matter.

General Changes—(*a*) *Degenerative and Necrotic*.—We have now to consider how the cellular colony which constitutes the whole body may be affected generally by such an invasion, whether the invasion be confined locally, either at the beginning or during the whole of its course, or there be at any period of the infection a general distribution of bacteria throughout the body. Here, as in the case of the local effects, the changes produced may be divided into degenerative changes in cells,

which may or may not end in cellular death; and, secondly, reactive changes, the feature of which is cellular activity. With regard to the degenerative effects of bacteria, these are very widespread and well marked in acute infections. Their importance is probably greatest when they affect the large solid vital organs—the heart, the kidneys, the liver—and it is to these that the pathologist's attention is naturally turned. The most common degenerations are cloudy swelling and fatty degeneration. In most fatal cases of infection one or other or both affections may be found—it may be in different degrees—in the organs named, and there is no doubt that cloudy swelling may be followed by the fatty change. Further, consideration of the presence of these degenerations in what may be called cases of accidental death during infections, such as follows perforation or hæmorrhage in enteric fever, shews that probably a considerable degree of degeneration may be recovered from. In some infections the degree of degeneration may be extreme; for example, in yellow fever the changes in the cells of the heart, kidney, and especially of the liver, may be so marked that the cytoplasm is enormously enlarged and almost completely composed of fat, while the serious interference with the vitality of the cells is shewn by the manifest acidophilic tendency of the nucleus, and by the tendency to destruction of the outline of the cells. As Kempner (153) has shewn for the bacillus of botulismus, these changes can be originated by poisons isolated from bacterial cultures. In addition to the fatty, other changes are found; sometimes, as in certain cases of small-pox, scarlatina, and septic disease, a loss on the part of the cellular protoplasm of its normal granular appearance (vitreous degeneration) has been noticed in the liver and kidney. In some severe infections a condition allied to coagulation-necrosis has been observed in the same organs, and there has also been seen a loss on the part of the nuclei of the secreting cells of their capacities for taking up basic dyes. In the heart certain special features are sometimes recognisable, as indeed might be expected from the highly specialised structure of the organ. The striation of the muscular fibres is often lost, the protoplasm vacuolated, and apparently the nucleus may divide. Further, the attachment of the muscle-cells to one another may be interrupted. These appearances are most marked in infections in which the products of bacterial action appear to have a special affinity for the cells of this organ, the best example of this being found in diphtheria. While the great solid organs are those the affections of which are probably of greatest importance from the standpoint of the body as a whole, the other organs of the body are also the subjects of similar changes well worthy of more investigation than has hitherto been bestowed on them. Thus, in animals dying from diphtheritic inoculation, a very marked feature is the swelling and congestion of the suprarenal glands, the significance of which is unknown. Again, in certain infections, of which hydrophobia may be taken as a representative, changes occur in the central nervous system which, as neuropathology advances, are becoming more and more recognised as definite in type (cf. Marinesco). In

the peripheral nerves the best example of the occurrence of changes is in the very common post-diphtheritic paralysis. Here, according to Sir W. Gowers, there is segmentation and breaking up of the white substance of the nerves with multiplication of the nuclei of the sheath.

One degeneration may be alluded to, though it is usually considered in relation to the inflammation with which it is usually associated, namely, the change allied to cloudy swelling which often occurs in infection in the capillaries or smallest arterioles. This often leads to rupture of the affected vessel, and hæmorrhage into the tissues. It is specially marked in the kidney in many cases of scarlet fever, it may occur in the liver in small-pox, in the brain in hydrophobia, and in the skin in connexion with such exanthems as typhus fever, small-pox, scarlet fever.

In chronic infections, such as the infective granulomas, other degenerations, in addition to those already alluded to, occur; of these the best example perhaps is the hyaline degeneration of connective-tissue fibres, especially in connexion with the vascular system, in tertiary syphilis. Here also may be mentioned the waxy degeneration, which may also occur in the granulomas, though whether this is in reality a true cellular degeneration, and not merely evidence of a pathological cellular excretion, is open to question.

Of great interest and importance are the changes produced in the blood in infections. During such diseases evidence can often be obtained of the existence of a very definite degree of anæmia, the red blood-count falling, it may be, by several millions per c.mm. In acute infections the diminution is probably due to destruction of red blood-cells, as poisons having this effect have been obtained from certain pathogenetic bacteria. In more prolonged infections interference with the erythroblastic function of the bone-marrow may account for part of the change. Other alterations may occur in the blood-fluids, such as changes in the saline content and in the coagulation-time, but their significance is not clear, as the variations have not yet been sufficiently investigated. The changes in the leucocytes will be referred to below (p. 27).

(*b*) *General Reactive Changes.*—The general reactive changes which indicate cellular activity are also of importance. In the first place, these are of the nature of inflammatory conditions affecting the connective tissues of various organs, and present generally the phenomena of an inflammation often slight in extent, but of a very diffuse character. In many instances they may be associated with a general distribution of the infective agent. Thus, for instance, we cannot say that this may not be the case in the nephritis of scarlet fever, and in the changes suggestive of acute inflammation seen in the liver both in this disease and in small-pox. In diphtheria, in which the main effects are found at a distance from the focus of bacterial multiplication, changes of a similar kind have been described in the heart, as also in enteric fever, where a toxic element is probably also pronounced. With regard to changes of this kind some investigators have taken the view that these are limited to alterations in the vessels of the nature of active hyperæmia and to leucocytic

exudation, and that the latter is secondary to degenerations of the parenchyma of the organ, and is related to the necessity of removing either the degenerated cells or their pathological excretions. Changes, most probably of a toxic origin, of the nature of an active hyperæmia are responsible for many of the skin eruptions so common in infective diseases. Affection of the arteries and veins of the body of an inflammatory character are also observable in some infections, and when combined with degenerations of the endothelium may play a part in the production of the intravascular—especially intravenous—thrombosis observed in certain infective diseases. Important changes also occur in the nervous system in consequence of allied processes. In many acute nervous affections of infective origin, in addition to the degenerative effects already noted, congestion of blood-vessels and leucocytic emigration may be observed, as in rabies (Roger, 291, p. 796), but in certain cases this interstitial inflammation may be the primary condition. This is especially true of the multiple neuritis of influenza, diphtheria, scarlet fever, erysipelas, and other infections; chronic forms of the same class of pathological change occur in leprosy and syphilis. Widespread changes of a reactive character are also seen in the alimentary and respiratory systems even when these systems are not otherwise involved in the infection. This is evidenced by the occurrence of catarrh—a shedding of epithelia with an unwonted proliferation of the cells whose function it is to replace normal waste.

Changes in the Blood and Hæmopoietic System.—Having considered the reactive changes of an inflammatory nature, we must now turn to an even more important group of reactions regarding the true nature and significance of which it is impossible to speak with any degree of definiteness. It has been long known that in many infections there is an increase in the number of white blood-corpuscles in the circulation. That this is not due to a decrease of the total volume of the blood is indicated by the fact that the relative proportion of white cells to red cells rises, while the absolute number of the latter is often actually smaller than normal. Counts of from 15,000 to 30,000 or over are common in septic conditions, abscess-formation, pneumonia, etc. Usually not only is the total number of leucocytes increased, but there is an increase of one group, often the polymorphonuclear cells. Sometimes, as in enteric fever, while there is no leucocytosis, and even a diminution of white cells (leucopenia), there is a disturbance of the normal proportions of the different white cells. Thus, in enteric fever the lymphocytes are relatively increased, and a similar state of affairs obtains in small-pox, especially in milder cases occurring in the vaccinated. We are here concerned with the explanation of the occurrence of these alterations, and not with their possible prognostic significance (see "Clinical Examination of the Blood," Vol. I. p. 679). In the ordinary case of a leucocytosis with an increase of polymorphonuclear cells the question arises, "Whence comes the increase?" The researches of Prof. Muir (250) and others have demonstrated that the origin of these cells in the body is in the red marrow,

and in that situation there are large stores of such cells from which may be drawn the extra cells which pass into the circulation in physiological leucocytosis, for example, after a meal. Under certain conditions of infection the marrow may be drained till it is almost free of this type of cell, but, as Prof. Muir has shewn experimentally in animals and from observations on naturally infected men, a further event may occur, viz. active proliferation in the bone-marrow of the neutrophil myelocytes — the progenitors of the neutrophil polymorphonuclear leucocytes. Fresh stores of leucocytes are thus formed, and so active may the process be that in a very few days not only may the red marrow exhibit the greatest embryonic activity, as is evidenced by the occurrence of numerous mitotic figures in the myelocytes, but the yellow marrow may be encroached on by the actively proliferating cells, which infiltrate and cause an absorption of the fat-cells. A very great part of the medullary cavity of a long bone may thus come to be occupied by newly formed and active leucoblastic tissue. Not only in the marrow but in the other hæmopoietic organs is there evidence of cellular activity. The functions of the spleen constitute one of the problems, or probably a series of problems, of great complexity. The organ has long been recognised as being liable to change in infections. The enlargement occurring in anthrax in cattle has given to the disease one of its names, and the increase in size which occurs in typhoid fever in man is recognised as a clinical feature of importance in diagnosis. In other infections evidences of some change, either in size or character, are well known. The importance of the organ in infection is in nowise affected by the fact that its removal is an operation which may have little or no apparent effect either on the ordinary health of an animal or on resistance to infectious disease. The multifarious forms of its constituent cells argue that the organ has complex functions, of which phagocytosis is the best recognised. After the injection of pigments into the blood the cells in the spleen are seen to take them up in a marked degree, and bacteria are often found in large cells with hyaline protoplasm—probably either the endothelium of the pulp-sinuses, or cells derived from them. The proliferation of these cells and their phagocytic activities were thoroughly investigated by Mallory in typhoid fever, and his results have been confirmed for other diseases. They are classed by Metchnikoff among the *macrophages* (*vide* art. "Inflammation," Vol. I. p. 733). It may be in consequence of the phagocytic action not being sufficient to destroy the bacteria taken up that the spleen may be found, as sometimes occurs, *e.g.* in anthrax, to be a special site of bacterial growth. These cells, however, are also probably concerned in the destruction of other cells whose cycle of functional activity has come to an end. In infections they may be observed to contain numerous red blood-cells, and also polymorphonuclear leucocytes. Evidence also exists of extracellular digestion, both of red and white blood-cells in the organ, so that it is probable that the secretion of digestive fluids forms a function of some splenic cells. Prof. Muir has observed in infections active proliferation—as evidenced by mitosis—of

these endothelial cells, and also of hyaline leucocytes in the sinuses. Further, there is a proliferation of special cells, larger than lymphocytes, and with abundant and basophilic protoplasm, which are found in a zone round the Malpighian bodies. In the lymphatic glands of the body there is less evidence of activity, and the change is more of the nature of an ordinary inflammation, with polymorphonuclear exudation from the vessels; but in certain infections there is also an increase of lymphoid tissue in the germinal areas, which are the ordinary sites of the genesis of the small lymphocytes of the blood, and here also proliferation of the endothelial lining of the lymph-sinuses gives rise to cells similar to those described in connexion with the pulp-sinuses of the spleen.

From a consideration of these facts we can now understand how it is that changes occur in the blood in infection. No doubt, at first, the blood-cells, so far as they are amœboid, are drawn from the storage centres by chemiotactic influences, but later there is an acute proliferation originated in the blood-forming tissues, and thus an increased supply of cells is ready to pass into the blood either under these chemiotactic influences or by mechanical means when cellular contractility is absent or weak, as in the case of the small lymphocytes. These blood changes constitute the most striking and, it may be, the most important element in the general changes occurring in the body in infection. In a local inflammation caused by bacterial infection, the migration of leucocytes from the vessels under chemiotactic influences has often been looked on as constituting the essence of an inflammation. But only in a very limited and local infection does this diapedesis alone affect the white cells circulating in the neighbouring blood. Whenever an infection becomes severe and begins to manifest general effects either by the general distribution of bacteria or while, as in pneumonia, the bacteria are still largely or entirely confined to one locality, then the local leucocytic reaction becomes but a part of a general reaction, which affects not only the leucocytes of the circulating blood, but the blood-forming organs themselves. How far-reaching the effects of this reaction may be in modifying the vital actions of cells and the constitution of the bodily fluids we shall consider under the heading of immunity.

The effects of the action of infective bacteria on the structure of the body may be thus summed up:—

(1) *Local*: (*a*) Cellular degenerations.
(*b*) Cellular activity—occurrence of inflammation, including leucocytic exudation.

(2) *General*—(*a*) Cellular degenerations.
(*b*) Cellular activity.
(*α*) Diffuse effects of an inflammatory type.
(*β*) Proliferative activity of blood-forming organs.

The Toxic Effects of Bacteria.—Besides the recognition of the effects produced by bacteria, the paramount truth which must be emphatically insisted on here is that the chief effects of bacteria are not dependent

on the actual presence of the bacterial cells. As we shall point out immediately, a general distribution of bacteria in the body in human disease is rare, and yet the occurrence of general effects, even when the bacteria are confined to one part of the body, is the rule. To explain this occurrence several hypotheses were formerly advanced, such as, for instance, that the bacteria used up the food of the tissues, or that they cut off the blood-supply. But, as we shall presently see, the isolation from bacterial cultures of chemical substances capable of originating specific effects has led to the view that such poisonous materials, the products of bacterial protoplasm, are responsible for the distant effects which bacteria produce. Before considering these poisons there is a matter to which we must allude.

B. Changes in Function

Such diverse structural affections as we have described cannot but have a serious effect on the functions of the organs concerned. Slight local infections, especially of the extremities, beyond affecting movement, cause comparatively little functional interference. Even a local infection, however, may have serious effect if it involves an internal organ. Thus, infective endocarditis may rapidly produce serious effects by causing valvular incompetence, and a suppurative condition in the kidney, secondary, for instance, to vesical infection, may set up degenerative changes in the renal parenchyma which may be followed by arrest of its function. The interferences with function caused by general effects are, however, much commoner and more serious. Their consideration presents a problem of great complexity. In even comparatively slight local infections, and in nearly every acute general infection, there occurs the interference with heat-regulation which causes the bodily temperature to rise; in other words, which produces fever. The pathology of fever is still far from being placed on a secure basis (*vide* art. "Fever," Vol. I. p. 818), and many questions arise. The fever may be the expression of increased metabolism of bodily cells caused by bacterial poisons, but increased metabolism from pathological changes very similar to those of bacterial infection, such, for instance, as occur in phosphorus poisoning, is not associated with fever. On the other hand, the raising of the temperature, due it may be to diminished output (however this diminution is caused), may originate the changes in the cells. But in whatever way the elevation of the bodily temperature may come about, there is an increased breaking up of the bodily tissues. The question for consideration is whether this is due to the direct action of the bacterial poisons on the tissue-cells, or indirectly due to the action of these poisons on a central heat-regulating mechanism. Till this is settled we can have no clear conception of the etiological relationships of many of the functional changes observed, and our knowledge of what occurs in the fever of infection throws little light on the matter. It is possible that bacterial poisons may have direct effects on tissue-cells and lead to

increased metabolism and increased production of heat. For during the early stage of an infective fever while the temperature is still little above normal it is probable that there is increased production as well as increased loss of heat. On the other hand, the following observations indicate an effect on a heat-regulating mechanism. It has been shewn by numerous investigators (Roger (291), Krehl and Matthes (171)) that it is possible to isolate from bacterial cultures poisons giving rise in small doses to fever, which may or may not be followed by recovery, while larger doses invariably cause collapse, unaccompanied by fever and resulting in death. Undoubtedly similar facts obtain in natural infections. In scarlatina, for instance, while in the less severe forms fever is practically an invariable accompaniment, there is the malignant form,—undoubtedly toxic in nature,—in which the individual attacked rapidly succumbs from collapse without any fever [*vide* p. 433]. Further, and now we must speak with the greatest reserve, it is possible that part of the increased heat produced in fever may be the expression of the increased work done by the bodily cells in that increased cellular activity which constitutes the reaction against infection.

Apart from general effects on metabolism certain organs are functionally affected in a special degree. For instance, we have the tendency to cardiac weakness in diphtheria and pneumonia, the paralytic effect on the nervous system in one form of hydrophobia, and the spasms of tetanus. These last two examples are of special interest and importance in that they are not associated with any great structural lesion in the parts affected. Similar functional disturbances probably account for the delirium of infective fevers, and even for certain of the convulsive seizures which occur. With regard to the heart and circulatory system the well-known changes in the character of the pulse brought out by sphygmographic tracings in infections indicate the alterations in function produced. Attempts have been made to study these experimentally, but apparently not in animals suffering from natural disease. Roger studied the effects on the frog's heart of poisonous substances derived from bacterial cultures. Apart from the objection that these substances were very probably modified by the means of separation adopted, the experiments are open to the criticism that the doses given were enormously in excess of the amount of a bacterial poison acting on the heart at any particular stage of a natural illness. Of interferences with the functions of other organs the kidney is the best example. Here, with absence of evidence of actual pathological change of such degree as to cause death or detachment of the secretory cells, there is often evidence of loss of function in the presence of albumin in the urine. This may be an accompaniment of changes such as cloudy swelling. When there is actually cellular desquamation the albuminous excretion may be much more apparent. Acute inflammation of the kidneys may also, as in scarlatina, be accompanied by rupture of capillaries and the appearance of hæmaturia. In chronic degenerations, such as waxy degeneration, the kidney function is much affected along similar lines. The excretion of urea may also

be interfered with both in acute and chronic infectious disease. Usually in such cases there is structural change, but in very acute conditions this may be absent, and yet the suppression of the kidney function may lead to death. Little can be said as to the nature of functional interferences with other organs, though these undoubtedly exist. Their investigation, however, is complicated by two conditions: first, our ignorance of the essential nature of fever, which prevents our estimating the parts to be assigned to direct bacterial action on organs and to the effects of the mere elevation of bodily temperature on general metabolism. Secondly, in nearly every infection the intake of food is diminished, and thus it is difficult to compare the metabolic processes in such a condition with those obtaining in health.

From what has been said regarding the diverse interferences with structure and function which bacteria may originate, it will be readily understood that death, when it occurs from bacterial disease, may be due to a great variety of causes. Sometimes mere local effects, such as, for instance, an inflammatory œdema of the glottis, may cause death. Most usually, however, death is due to general conditions. It may come from mere rise of bodily temperature, from poisoning of the heart, from interference with the kidneys leading to the suppression of their functions, from interferences with general metabolism, and (especially in chronic infections) from the drain of nutriment from the blood, such as occurs in waxy disease of the kidneys.

The Distribution of Bacterial Lesions

In dealing with infectious disease, a series of widely differing phenomena must be accounted for. This is chiefly due to the complexity of bacterial action, but the varied distribution of bacteria in the body constitutes an important factor. In the first place we will consider some of the ascertained facts regarding this distribution of the bacteria.

In such a disease as tetanus the bacteria are entirely confined to the place of infection, there never being the least evidence of their spreading to other parts of the body. Even in the similar case of diphtheria where there is a pronounced local manifestation of activity the bacteria are confined locally. This is a very common occurrence in infection—local effects, local distribution of bacteria, and yet general metabolic and, it may be, even structural effects. In fact it is comparatively rare for bacteria to have a pathogenetic action in the body without some general disturbance, however slight that disturbance may be. Sometimes a modification of a local infection may be observed, in that the site of the local manifestation of bacterial growth may be some distance from the point of inoculation. For example the *Diplococcus intracellularis meningitidis* probably gains entrance to the cerebrospinal meninges through the cribriform plate of the ethmoid from the nose, in which situation they produce little or no pathogenetic effect. Again, in some cases of infection of bones or joints by pyogenetic bacteria the primary

site of infection, as indicated by a local reaction, may be sought for in vain post-mortem.

At the other extreme are cases in which with, it may be, little local reaction, the bacteria gain an entrance to a part, multiply with extraordinary rapidity, reach the blood-stream either directly or through the intermediary of the neighbouring lymphatics, multiply there also, and are found in every tissue of the body. Death in such cases invariably results. The condition is known as septicæmia, and, although usually only applied to cases in which a general distribution of the pyogenetic cocci occurs, the term in strict scientific phraseology must be extended to include similar affections caused by such organisms as the plague bacillus and the *B. anthracis.* In man a general septicæmia is uncommon; it is best seen in the septicæmic form of plague and in some rare cases of streptococcal infection. It is more usual in man to have a vigorous local growth succeeded by general effects of a purely toxic character.

There may, however, occur the development of secondary foci of growth caused by the settling down of escaped bacteria and the elaboration of poison by them. From the original local nidus in an acute infection the bacteria may pass into the neighbouring lymphatics. They may be caught in the nearest lymphatic glands, and set up a reaction there which may be the final manifestation of the disease, as in the frequently occurring abscess in the axilla secondary to a poisoned wound of the hand. They may, however, pass beyond the glands to set up other foci, it may be with a fatal termination. Sometimes the spread from a local nidus is through the veins (rarely, for obvious reasons, is there the opportunity for spread by arteries). Bacteria may gain admission to veins directly by being mechanically introduced into an injured vein in the local lesion. More frequently the local bacterial action affects the wall of a neighbouring vein, and the bacteria grow into the coats of the vessel. The vitality of the intima suffers impairment, leading to thrombosis; the bacteria grow in the thrombus, cause it to soften, and thus they may be carried into the circulation. This accounts for the occurrence of the pneumonic conditions which constitute a grave danger to life when they arise secondarily to local infections, such, for instance, as suppurative periostitis. The escape of a few bacteria into the blood in local infections is probably more common than is usually supposed. It is excessively rare in man to be able to demonstrate bacteria microscopically in the blood. But if, during an infection, a considerable quantity of blood, say 5 c.c., be aseptically withdrawn from a vein with a hypodermic syringe and incubated, evidence of the presence of the organism associated with the infection may be found. In chronic infections, such as tuberculosis, the principles of the distribution of the causal bacteria are the same. Spread may take place either by the lymphatics or by the blood-stream, and in both cases, especially in the latter, an enormous number of secondary foci may of course be developed.

In certain cases a spread of infection from one part of the body to

another may take place by transference of bacteria along natural free surfaces. Thus infection of one part of the skin from another is common; the rupture into an air-cell of a tuberculous focus in the lung may lead to infection by aspiration of the bacilli into other parts of the lung; the swallowing of tuberculous sputum may lead to ulceration in the intestine. Similar processes may be at work in the spread of bacterial infections from the urethra and bladder to the kidneys and testicles.

The spread of infective bacteria may to some extent be determined by certain organs of the body constituting a better food-supply for bacterial growth, or the conditions of local circulation may come into play. Thus, in the spread of pyogenetic cocci as from the cardiac valves in infective endocarditis, these are much more apt to settle in the kidneys, the joints, and in certain cases (especially in the artificial inoculation of animals) in the serous cavities than in other parts of the body. In glanders, on the other hand, the bacilli are prone to settle in the joints and in the skin, and of the solid organs the spleen is said to be more frequently affected than the kidneys.

The Poisons formed by Bacteria

Historical.—Study of the pathological effects of bacteria emphatically established the position that bacteria can act at a distance from the site of their multiplication in the body. The proof that such an action occurs rests on the isolation from bacterial cultures of substances capable of producing the same changes that would follow the injection of the cultures. The earliest demonstration of the poisons produced by and excreted by bacterial cells is found in the work of Roux and Yersin (295) on diphtheria. These observers shewed that if cultures of the diphtheria bacillus were filtered germ-free through an unglazed earthenware cylinder, the filtrate was toxic, and produced, according to the dose, rapid death or a more protracted illness during which the paralyses, so characteristic of natural diphtheria, frequently occurred. Similar results were obtained with tetanus by Kitasato (155). To the early part of the same period belongs the work of Brieger (45) on certain poisons, chiefly alkaloidal in nature, called ptomaines, which were isolated by him from putrefying flesh and also from bacterial cultures. Such alkaloidal poisons probably do exist, as has been shewn by Brieger, Vaughan and Novy (334), and others, and occur in connexion with the poisonous effects of flesh, fish, cheese, and so forth (see "Food-poisoning," p. 855), but it is practically certain that alkaloidal bodies play a subsidiary part, if any part at all, in the pathogenetic action of bacteria. Brieger and Fraenkel (47) next, by treatment with alcohol and with other precipitants of proteids, isolated from cultures of the diphtheria bacillus certain albuminous substances, which they termed toxalbumins and regarded as the toxic agents; certainly part of the true toxic principle was thus precipitated. Prof. Sidney Martin (222) established the capacity of these bacteria to produce fermentation products such as albumoses, and further shewed

that the breaking-down process could proceed even further and give rise to alkaloidal bodies (in anthrax) or organic acids (in diphtheria). Further, he isolated from the spleens of individuals dead of diphtheria albumoses, which, when given in repeated doses, produced in animals paralyses of a post-diphtheritic type. Since fermentation undoubtedly occurs in bacterial cultures, Prof. Martin put forward the hypothesis that in diphtheritic infection a double process was at work. He conceived that in the membrane the bacilli gave rise to a ferment, and that this ferment, being absorbed into the body of the infected animal, set up a proteolytic change, resulting in the production of toxic albumoses, which were the active agents in producing the intoxication-phenomena. Whether the toxic agents are really albumoses or not, there is no doubt that they can be obtained from cultures by chemical methods appropriate to the isolation of albumoses. Brieger and Boer (46) state that they have obtained specific toxic materials which give no proteid reaction, but their experiments have not been repeated. Uschinski's (330) observation that the diphtheria bacillus could grow and could produce its poisons in urine (free from proteid) would rather point to the true poisons being formed intrabacterially and not secondarily from material present in the food mediums. The observation does not, however, exclude the possibility of these poisons being albumoses, for the building-up processes which result in the formation of the higher albumins of the bacterial protoplasm might be followed by a metabolic breaking-up of that protoplasm into lower proteids.

The Toxins.—All attempts to obtain bacterial poisons in a condition of purity have hitherto been unsuccessful, and for a long time past bacteriologists have been forced to confine their attention to impure bacterial products, which, though containing the poisons, contain much else. Study has thus been directed rather to the toxicological action of these impure mixtures than to the substances to which the toxic action is really due. Since these poisons possess features which mark them off from well-known toxic agents like the toxic alkaloids, glucosides, it is usual to denominate the bacterial poisons by the indefinite term *toxins*. We cannot go far in our study of these toxins without recognising that poisons of different kinds are produced by bacteria. From lack of precision in the present state of our knowledge it is, however, difficult to classify these varieties and to speak clearly regarding them. An outstanding feature recognised soon after the first work of Roux and Yersin was that while, in the case of many bacteria, toxins could be easily separated from fluid cultures by filtration through porous earthenware, in the case of others, of which the anthrax bacillus may be taken as an example, no toxic filtrates could be obtained, although the intoxicating qualities of the bacteria in actual disease appeared undoubted. This led to the idea that in some cases the toxins readily pass out of the bacterial protoplasm into culture fluid, while in others either this passage does not occur or the organisms cannot form in culture fluids the toxins which they elaborate in the animal organism. Leaving the last

possibility out of account, it has been usual to differentiate between extra- and intra-cellular toxins. The terminology is unfortunate, for the extra-cellular bacterial toxins have been found merely to be examples of a class of poisons widely distributed in the animal and vegetable kingdoms. The situation is rendered still more difficult by the fact that in certain bacterial poisonings representatives of both groups are probably actively engaged. For convenience we shall speak of the extracellular toxins and allied poisons as the diphtheria group, and apply the term intra-cellular toxins to those usually described under this name, but we must not be supposed to commit ourselves to the position that the poisons of the two groups differ fundamentally from one another.

(*a*) **The Diphtheria Group of Toxins.**—(*α*) *Bacterial Toxins.*—The chief bacterial members of this group are found in the crude toxins derived from cultures of the *B. diphtheriae* (Roux (292)), the *B. tetani* (Kitasato (155)), and—of much less importance—from the *B. botulinus* (Kempner (153)). The bouillon cultures are grown under conditions which experience has shewn to produce the strongest toxins. These conditions vary in different cases. Much depends on the constitution of the medium, and on the temperature of growth, and on the period elapsing before filtration. Sometimes strains of bacteria are met with which will not produce toxins under conditions usually favourable. Generally speaking, in any bouillon culture, there is a period of increasing toxicity until a maximum is reached. This is succeeded by slow disappearance of toxin, and ultimately very old cultures may be found to be quite innocuous. After growth the cultures may be filtered through unglazed earthenware and the filtrate kept covered with a thick layer of toluol. Sometimes filtration is not resorted to; the culture may be merely repeatedly shaken up with a considerable quantity of toluol until control cultures shew that all the bacteria have been killed. Again, the fluid may be simply allowed to stand to deposit the bacteria, or it may be centrifugalised and the upper layer used as the crude poison. When the organism forms spores, as occurs with the tetanus bacillus, this treatment will not kill the spores, and the toxin thus produced cannot be used for animal experiments. Again, in a culture—filtered or unfiltered—a concentration of the toxin may be accomplished by adding crystals of ammonium sulphate to saturation, setting aside for twenty-four hours at 37° C., and then skimming off the precipitated proteids (which, from the density of the solution, float on the surface). These may be dried *in vacuo* over sulphuric acid and stored in the dry condition. Further attempts at purification being, as we have seen, impossible, the properties of the poisons can only be studied by the investigation of the toxicological reactions of the crude fluids. In the cases of the specific disease-producing poisons of diphtheria and tetanus this is done by estimating the smallest amount (minimal lethal dose, or, briefly, "M.L.D.") which will kill a guinea-pig of 250 grammes weight on the fourth day after inoculation. This is, of course, a purely artificial standard, but it is founded on the general principle that if an animal survives this length

of illness it will probably either survive altogether or die only after a chronic illness. The strength of a toxin is always measured in terms of this minimal lethal dose, and such a standard is adopted with all toxins, though of course the type of pathological effect to be taken as the minimal one must be varied with the toxin under consideration.

The study of the bacterial toxins of the group under consideration has revealed the possession by them of certain characters. Thus they are all dialysable, they are all precipitable from solution by alcohol and ammonium sulphate, and, generally speaking, they are, as has been said, separable by any method capable of separating albumoses from mixtures of proteids. Generally speaking, they are inclined to lose their toxic properties when heated, though here there are considerable individual differences. Thus the diphtheria and tetanus toxins lose their toxicity after half an hour's exposure to a temperature of 55° C., while the toxin of the dysentery bacillus is not affected till a temperature of 70° C. is applied for an hour. Further, these poisons are very susceptible to the action of the digestive ferments, so that large quantities can often be taken into the stomach without any morbid effect being produced. Their toxic properties are also removed by many chemical substances, and especially by acids and alkalis. None of these agencies, whether heat, digestive ferments, or chemicals, necessarily break up the poison molecule. They merely diminish or destroy its toxicity. With regard to the pathological effects of these poisons, one of the most striking features is the frequent occurrence after inoculation of a period of incubation, during which the poison appears to be latent in the system of the animal attacked. This period varies with the dose, but in the case of bacterial toxins always exists, though at present we can give no explanation of the phenomenon. But perhaps the most characteristic feature of this group of toxins, which probably more than any other marks them off as a separate group of chemical substances, is that if successive non-lethal doses be injected into an animal, it is found that in the serum of that animal there appear substances which can neutralise the toxic action of the toxins. These substances are the antitoxins. This antitoxin-formation probably does not occur with other poisons. Besredka (28) has described such a phenomenon in connexion with immunisation against arsenic, but his experiments might have another interpretation. Morgenroth (248) could not find evidence of an antitoxin-production in immunisation against morphine. It is the recognition of a characteristic antitoxin-production which justifies the extension of the limits of this group to include poisons of non-bacterial origin. The chief toxins thus brought into the group are found among the snake-poisons, but examples are found in the less important scorpion- and spider-poisons and among the vegetable poisons in the toxins, ricin and abrin, derived from the castor-oil bean and the jequirity seed respectively. Evidence from the chemical side pointing to the probability of the relationship of these poisons with the bacterial poisons had previously been obtained. Thus Weir Mitchell (243) had concluded that the snake-venoms were albumoses. The fact of the

association of the diphtheria group of toxins with the development of corresponding antitoxins has been found to shed light on the nature and mode of action of these toxins. This necessitates the postponement of the consideration of many questions which naturally arise here, till we can deal at the same time with the properties of the antitoxins. The pathological effects of the diphtheria and tetanus toxins may be considered, as these are by far the most important bacterial members of this group of poisons. One feature deserving attention is their great potency. Thus it is not uncommon to obtain a tetanus poison which will kill a guinea-pig in a dose of ·001 c.c. of the fluid filtrate. Ehrlich found with crude ricin that the minimal lethal dose for a guinea-pig was ·00004 gramme per kilo. of body-weight, and Major Lamb (174*a*) has calculated that in man the fatal dose of crude cobra-venom is probably ·015 gramme. Again, these poisons rather tend not so much to upset the general bodily metabolism as to produce effects on special tissues. It is this point which, in the first instance, constituted the proof that the diphtheria and tetanus bacilli acted through the agency of extra-cellular poisons. The purest example of toxin action is found with tetanus toxin. Here, whether the dose be great or small, the spasm-producing action of the toxin is dominant, and it is this which causes the fatal result. In guinea-pigs, after inoculation and the lapse of the incubation-period, stiffness and spasms appear, commencing in the limb nearest to the point of inoculation, gradually extending to the whole body, and ending in a fatal spasm of the glottis. This is identical with what occurs in infection of the guinea-pig with the bacillus itself, and it closely resembles the natural disease in man. In the case of the diphtheria toxin the effects are identical with those occurring in bacterial infection, but the phenomena produced have suggested that the crude diphtheria toxin might contain at least two poisons having somewhat different actions. If a comparatively large dose of the toxin be administered to an animal it will rapidly become ill, suffering with œdema at the point of inoculation and with slight fever and general prostration, marked especially by a cardiac debility, which will be the direct cause of death. With a smaller dose the preliminary signs of disease will be manifested in milder form: there will be some falling out of the hair at the site of inoculation and perhaps some local necrosis, but the marked feature will be delayed for some days, when a general muscular paralysis of a more or less widespread character will supervene, and the animal may die from affection of the muscles of respiration. From the standpoint of pathological anatomy there may often be little to remark in animals dead from the effects of these poisons; in the heart-muscle and its nerves the changes may be very slight in the acute illness; in the chronic condition well-marked changes in the peripheral nerves are present. In acute cases of poisoning, either by diphtheria or tetanus toxins, the central nervous tissues which bear the brunt of the disease may exhibit no change certainly observable by ordinary microscopic methods, and the only phenomenon to be seen

may be the occurrence of vascular congestion. Sometimes the organs of the body other than those on which the poisons actually work shew likewise little change. Sometimes, however, they exhibit cellular degenerations, and in diphtheria Komotski (166) has shewn that these degenerations occur in the endothelium and adventitia of vessels all over the body. There may also be reactive changes. Both Gabritschewski and Besredka (26) record leucocytosis as common in both natural and experimental diphtheritic intoxications, especially when these are non-fatal, and they consider this important from a prognostic point of view. According to Trambusti there may be proliferative activity in the leucoblasts of the bone-marrow, and Metchnikoff (233) has shewn that a similar leucocytosis occurs when non-fatal doses of tetanus toxin are administered. These observations indicate that the part played by the bodily tissues in bacterial intoxications is not merely passive. Whether the reactive changes are to be attributed to the action of the special characteristic toxins is a question which must be reserved. In diphtheria there is nearly always interference with metabolism, as is indicated by the presence of fever. In the other bacterial poisons of this group, *e.g.* botulismus poison, there is less selective action and a more general degenerative effect in the solid organs. As we shall see later, when dealing with the interactions of diphtheria toxin and antitoxin, investigation has shewn that the apparently different effects are really produced by a group of allied poisons and not by essentially different toxins.

That toxins of different kinds may be present in crude bacterial filtrates is well shewn by the case of the crude tetanus toxin. Here the predominant element is always the spasm-producing poison—the tetanospasmin of Ehrlich—and it may be present alone. In certain crude toxins, however, there is evidence of another poison, which has the capacity of inducing hæmolysis in the red blood-corpuscles of certain animals. This was called by Ehrlich tetanolysin.

Hæmolysis may be produced in a variety of ways, and as the occurrence will be referred to again and again in our future discussions, we may speak of the process in some detail. If red corpuscles be placed in isotonic salt solution the mixture will present a reddish turbid appearance from the corpuscles being merely suspended in the fluid. Microscopically the cells will undergo no apparent change. If, however, instead of saline solution, distilled water be employed, in a few seconds a perfectly clear hæmoglobin-tinted fluid results. Microscopically the corpuscular elements are just visible as round, translucent, greatly swollen bodies. The occurrence is usually explained by supposing that the saline content of the cell-juice has by osmosis caused a rapid absorption of water through the cell-membrane, and that the hæmoglobin either passes out by diffusion or it is liberated by actual rupture of the cell. While the greater part of the hæmoglobin thus passes into solution, there is evidence that in certain circumstances the solution of the rest of the protoplasmic content of the hæmolysed cell is not complete. Bordet (39) and Dr. Haldane (142) have shewn that on the addition of salts to a hæmolysed mixture a turbidity may again

appear, and on microscopic examination this is found to be due to a shrinking together of the still existing remains of the protoplasmic network of the cells. These remnants may shew evidence of retaining a certain amount of hæmoglobin entangled in their substance. It thus appears as if the osmotic capacities of the cellular framework had not been altogether destroyed. It is, however, doubtful whether all the phenomena which go under the name of hæmolysis are of the same nature. Bordet, speaking of the case, to which we shall have frequently to refer, where a blood-serum possesses hæmolytic power, states that if salt be added to a solution containing hæmolysed corpuscles, the latter do not shrivel up and appear deformed, but regain their former round appearance. From this he infers that such an example of hæmolysis is not due to ordinary osmotic phenomena, but that here the cells have actually lost their capacity of behaving in an ordinary way so far as osmosis is concerned.

The occurrence of hæmolytic poisons has been observed in bacterial toxins other than that of tetanus. Thus Neisser and Wechsberg (255) have found such a toxin in the filtrates of bouillon cultures of staphyloccus pyogenes aureus. Marmorek (216) and also Schlesinger (307) have shewn that a similar toxin exists in cultures of the *Streptococcus pyogenes*, and similar observations have been made with regard to certain vibrios by Kraus and Ludwig, and by Madsen and Walbum (200). These results may have a bearing on the explanation of the anæmias which, as we have seen, are so characteristic of many bacterial infections. Reference may also be made here to a poison found by van de Velde in staphylococcus cultures, and still more markedly in the fluid of the pleural exudation of animals dead of staphylococcus infection. This poison has the properties of killing leucocytes in a few minutes, and has been named leucocidin. It evidently might play an important part in the pathogenetic action of the bacterium producing it. The observations of Denys and van de Velde (85), that an antileucocidin can be produced, probably justifies us in including it in this group of poisons.

(β) *The Snake-Poisons.*—The most complex of all the crude toxins of this group are, however, met with amongst the snake-venoms. Dr. C. J. Martin (220) has summarised our knowledge of the subject by saying that different venoms have been found to contain one or more of the following poisons :—A fibrin ferment ; a neurotoxin, with in many cases a special affinity for the cells of the respiratory centre ; a neurotoxin, with an affinity for nerve-endings in muscle, especially those of the diaphragm ; various bodies capable of dissolving cells (cytolysins), *e.g.* red blood-cells, endothelium of vessels (causing hæmorrhages), leucocytes, nerve-cells, and cells of many other tissues (each cell being probably acted on by a special toxin) ; an anti-bactericidal body ; a body preventing the action of fibrin ferment ; a body causing red blood-cells to adhere in clumps (agglutinin) ; a proteolytic ferment ; a body causing systolic standstill of the isolated heart. Every venom does not contain all these poisons, and the proportions in which the elements occur varies very much in different snakes. This largely accounts for the difference in effects produced by the bites of different snakes. Nearly all venoms contain the neurotoxic elements,

which are probably in nearly all snakes the most important poisons present, and are most frequently the cause of death in snake-bite (174). The poisons causing thrombosis are also very important. The hæmolytic poisons are widespread in their distribution, though the amount present in different venoms varies greatly. It has been shewn by Nowak that when death does not occur for some little time after snake-bite, serious degeneration of the solid organs may occur, of which the most characteristic is a grave fatty degeneration of the liver.

For further information as to the actions of particular venoms the reader is referred to the article on "Snake-bite," Vol. II. Part II. Here it need only be said that the neurotoxic poisons are probably in constitution clearly related to the diphtheria or tetanus poisons, while in at any rate certain of the hæmolytic poisons a complexity has been discovered which will be considered under the subject of immunity along with other scientific points relating to the nature of toxins. In conclusion, it may here be stated that many of the snake-poisons are much more resistant to heat than the bacterial poisons of the same group; and, further, that generally speaking no incubation-period is noticeable.

The *scorpion-poisons*, there is no doubt, are members of the diphtheria group of poisons, and according to some results must be closely allied to the snake-venoms. Their properties have been investigated by Dr. W. H. Wilson, who has shewn that they have chemical characteristics similar to those of the other toxins under consideration. Like many snake-poisons they are not easily destroyed by heat, and withstand boiling for some minutes. The symptoms produced by their injection into animals are twitching, lacrimation, salivation, and apparent paralysis, terminating in asphyxia. The effects, so far as the muscular system is concerned, are produced by an action not on the central nervous mechanism, but on the peripheral nerve-endings. There is an increase of excitability to direct stimulation, and an increase of the extent of contraction, with ultimately an apparent paralysis due really to fatigue. In accidental bites of man, above the age of 15, a fatal issue is rare, but in children death results in 60 per cent of the cases. The symptoms resemble the effects of artificial inoculation, namely, salivation, hallucinations, convulsions, weak pulse, gradually passing off in cases in which recovery occurs, or succeeded by coma if a fatal issue is threatened. Dr. Wilson found no evidence that hæmolytic or fibrin-forming ferments were present in the venom. Immunity can be artificially developed against the toxin, and this appears to be accompanied by antitoxin-formation. Calmette (63) was of opinion that the scorpion-poisons were closely allied to the snake-poisons in that the serum of a rabbit immunised against cobra-poison protected a guinea-pig against the fatal effects of the former toxin. This point requires further investigation.

Thus the snake-venoms and scorpion-poisons have very close relationships with the specific bacterial poisons, and it is very probable that many other animal poisons present a similar kinship. It is stated by Langer (178) that bee-keepers may develop immunity against the sting of

the bee, and Sachs (299) investigated a hæmolytic poison separated from the common garden spider, *Epeira diadema*, and found that an antitoxic serum can be developed against it. There is little doubt that the toxic hæmolytic properties of the serum of the eel, as described by Mosso (249), are traceable to toxins of this group. Possibly other poisons, such as those occurring in fishes and in the cutaneous secretions of amphibia, are of the same order, but further investigation is here necessary.

(γ) *Vegetable Toxins.*—With regard to the vegetable toxins, ricin and abrin, the interest is chiefly scientific, though cases of poisoning from eating castor-oil beans are recorded. The symptoms produced are great intestinal irritation, with sanguineous vomiting and diarrhœa, and fall of temperature, and the local injection of the substances causes intense irritation. Ehrlich (98) shews that ricin can agglutinate red blood-corpuscles, and that antitoxins can be produced against both ricin and abrin.

We thus see that there exists a group of poisons presenting certain similar characters, of which the most striking is the capacity readily to stimulate the formation of antitoxins. They all tend to have special actions on the body-cells, the cells of the nervous system and of the blood being the most sensitive to this special type of toxin. The probable constitutions of these toxins will be considered when the subject of immunity is dealt with. No clearer idea is obtained by speaking of them as ferments, for nothing is known about the nature of ferments. As we shall see later for similar bodies, there is evidence that a definite quantitative relationship exists between the amount of toxin acting and the degree of effect produced.

(*b*) **The Intracellular Toxins.**—We now pass to consider the intracellular toxins, or endotoxins as they are sometimes called. The application to pathogenetic bacteria generally of the filtering methods employed with the diphtheria bacillus, led to the discovery that in many cases it was not possible to separate toxic filtrates from ordinary bouillon cultures. Sometimes the filtrate was non-toxic, sometimes very large doses (as compared with the usual pathogenetic doses of the extracellular toxins) had to be administered in order to produce an effect. Usually the filtrates from old cultures, or cultures killed, say, at 60° C. and allowed to macerate, were more toxic than filtrates from young cultures. From these last, however, more toxic filtrates have been obtained by treating them with ammonium sulphate to saturation before filtration. The fact that whenever there was evidence that breaking up of the bacterial protoplasm had occurred there was an increase of toxicity of the filtered fluid, favoured the conclusion that under the ordinary culture conditions the endotoxins did not readily leave the bacterial protoplasm. This led to the employment of the fluid decanted from cultures killed by chloroform, or heat at 60° C., in which, after the death of the bacteria, a time was allowed to elapse for the cells to macerate and break up in the remains of the culture medium. In some instances, in order to study the effects of such toxins, merely the bodies of the bacteria killed

by chloroform or heat at 60° C. are employed. Various modifications of these methods have been used. Thus the intracellular toxins of the tubercle bacillus were obtained in the preparation of Koch's original tuberculin (tuberculin-O) by the concentration by evaporation of a glycerin-bouillon culture after the bacilli had been killed by boiling. The preparation was practically a glycerin extract of the bacilli. The second tuberculin preparation (tuberculin-R) was obtained by grinding up the dried bodies of the bacilli in an agate mill, treating with distilled water and centrifugalising. The deposit was again ground up, treated with water, and centrifugalised. This was repeated, and all the washings except the first were mixed and formed the tuberculin-R. This fluid thus contained certain of the endotoxins, and, according to Koch, contained the elements in the bacilli which were insoluble in glycerin. Again, the intracellular toxins of the typhoid bacillus have been obtained by grinding up the organisms with solid air, and expressing the fluids by hydraulic pressure (Macfadyen and Rowland (194)).

To turn to the nature and properties of the intracellular toxins we note that endotoxic filtrates have been treated with alcohol or ammonium sulphate, and toxic precipitates have been produced, so that, as with the extracellular poisons, we are probably dealing either with proteid bodies or with bodies entangled in proteid. Generally speaking, the endotoxins are not so sensitive to heat as the extracellular poisons, and in many cases they can be boiled for a considerable time without much injury (Wassermann (342), Marmorek (214)). It is right here to say that these so-called endotoxins may be substances which have no essential relationship to the pathogenicity of a bacterium. This view was held by Buchner (53), who by treating bacterial cultures, many of them of non-pathogenetic species, in various ways extracted from them substances which he called proteins, and which had fever-producing effects similar to those of the endotoxins. These results might with advantage be confirmed in the light of modern knowledge, but that pathogenicity need not necessarily be associated with the action of endotoxins is indicated by Dr. Klein's observation (156) that large amounts of anthrax and diphtheria bacilli killed by heat can be injected into an animal without producing any effect. It is probably of importance to note that the crude toxins may contain, besides the endotoxins and bodies derived from the media, other constituents of the bacterial protoplasm which, though non-toxic, may yet have some bearing on certain reactions which occur in the processes of immunisation. These additional constituents may play a part in stimulating the production in an immune animal of substances which are inimical to bacterial life.

The *general pathological effect* produced in animals by the injection of these endotoxins is to set up the non-specific alterations in metabolism (*e.g.* fever, etc.) characteristic of the action of the bacteria themselves. In contradistinction to what holds good in the extracellular toxins, there is no evidence from animal experiment of the occurrence of a period of incubation; the morbid effects follow almost immediately on their

introduction into the body. Artificial inoculation rarely reproduces any of the special characters of an infectious disease occurring naturally. Thus injection of the toxins of the *B. typhosus* produces an acute illness of comparatively short duration, quite unlike the ordinary natural disease. This, of course, may, however, be due to the difference in the dosage of the artificially formed toxin as compared with what happens in natural infections. A most important question is whether in any case these endotoxins can stimulate the formation of substances of the nature of antitoxins. This point will be dealt with in the discussion of the subject of immunity.

It is proper here to refer to the special case of endotoxin action occurring in what is known as the *tuberculin reaction*. Koch, working at tuberculosis, observed that if, into a guinea-pig already suffering from a local tuberculosis, a fresh quantity of tubercle bacilli be injected ulceration of the first lesion takes place; if the tuberculin-O, prepared from dead bacilli as above indicated, were used, then the lesions might undergo cure after the occurrence of ulceration. The view Koch took of what happened was that at the focus of tuberculous activity the bacillus was producing toxins causing slow death of the surrounding parts. The injection of the tuberculin, by introducing fresh toxins into the animal, caused a sudden concentration of the poison at the site of the infection, so that the cells already depressed were killed outright, and being cast off by the ulcerative process, carried with them the living tubercle bacilli of which the animal body was thus freed; healing could then take place. In human tuberculosis, the injection of tuberculin is followed in a few hours by malaise, fever, local redness at the focus of tuberculous activity, succeeded by ulceration. This is the so-called tuberculin reaction, and it was used for therapeutic purposes in human tuberculosis. While good results were obtained in some very superficial lesions, such as in lupus, it was inefficacious in others, and its application was not pressed. In these latter cases isolated tubercle bacilli, which had already passed into the surrounding tissues, probably were not only not cast off, but by the concentration of the poison were placed under conditions more advantageous for their growth. It is even doubtful whether the explanation given of the action of the substance was the correct one, for it was shewn by Krehl (171) and others that the tuberculin reaction could be caused by the injection of ordinary albumoses, lactic acid, and other bodies, so that if the reaction with tuberculin is caused by tuberculous toxins these share with other substances the effects they manifest. Moreover, Buchner (51) elicited a tuberculin reaction in tuberculous guinea-pigs by proteins derived from other bacteria, such as the pneumococcus and the non-pathogenetic *Micrococcus prodigiosus*. It cannot be said that we are in a position to speak with confidence as to the explanation of the phenomena of the tuberculin reaction which appears in some way to be bound up with the obscure problem of fever. In another granuloma, namely, glanders, a reaction of the same kind is produced by an extract of the *B. mallei* called mallein.

(*c*) **The Aggressins.**—Allusion has been made to the possibility that bacteria may produce in the body toxic substances which they cannot produce in artificial cultures. The idea that bacteria in the body elaborate materials which affect its resisting capacities had been mooted by Kruse in 1896. Recently the question has been further investigated by Bail (13), Weil, Kikuchi, and Hoke. The usual method has been to infect an animal with an organism such as the typhoid bacillus, the dysentery bacillus, the tubercle bacillus, the cholera vibrio, the *Staphylococcus pyogenes*, and after death to take the serous exudation which so often occurs in the resulting diseases, and centrifugalise it free of cells and relatively free of bacteria. To this fluid Bail and his co-workers give the name of the aggressin of the particular bacterium which originated it. They state that a quantity of this fluid, which by itself is incapable of originating disease, will when injected into an animal along with a quantity of bacteria increase the pathogenetic action of the latter. Thus in the case of the tubercle bacillus 100 mgrms. of a tubercle culture killed a guinea-pig in 18 days. The same amount with 4 c.mm. of tubercle aggressin caused death in from 22 hours to 3 days. According to Bail these aggressins act by paralysing the activities of cells which would naturally have an inimical effect on bacterial growth. The further investigation of these bodies will be of great interest.

In connexion with the action of bacterial poisons it is most important to remember that in any particular disease a number of poisons may be at work. Thus in a staphylococcus infection there are probably acting the intracellular toxins, a toxin destroying red blood-corpuscles, and a poison acting on leucocytes. Complex actions of this kind are very common.

Classification of Bacteria according to their Actions

We may now classify the best-known bacteria according to the modes of their pathogenetic action and their distribution in the lesions they produce.

(1) The acute infections. Here the bacteria, generally speaking, when they gain an entrance into the body, produce very manifest and it may be serious effects, often in the course of a few hours,—always in a few days. The phenomena originated are usually those of acute inflammation and degeneration, either focal or diffuse, and, in the former event, if the bacteria are carried in sufficient numbers from the original site to other parts of the body, similar foci of pathological change may be originated. Phenomena of general degeneration and general reaction, such as have been described, may be set up either by the diffusion of intracellular toxins or by toxins specially formed by the bacteria in the body. Sometimes an acute septicæmia, with a distribution of bacteria all over the body, occurs either with or without a previous local change at the site of inoculation.

This class includes the *Staphylococcus pyogenes aureus*, the *Strepto-*

coccus pyogenes, and the whole class of organisms associated with ordinary inflammations and suppurations, and usually called the pyogenetic bacteria. We must, however, also include the pneumococcus, the *B. anthracis* and the *B. pestis*, and also the morbid conditions set up by the artificial inoculation of the typhoid and cholera organisms in animals. It is a question whether the *B. typhosus*, when acting under natural conditions in man, should not be looked on as belonging to this class. It certainly sets up acute local degeneration and inflammatory changes in the intestine, and has also general effects. Its action must, however, be a somewhat special one, for although after death the bacilli are usually plentiful in the spleen and also in the liver, there are no changes in these organs at all analogous to the very marked local effects present in the intestine. This is all the more remarkable, since occasionally there is no other organism present in the suppurative foci, for instance those in connexion with bones, which occur as sequels of enteric fever. In some acute infections, ordinarily local, such as those set up by the gonococcus and the *Diplococcus intracellularis meningitidis*, the organisms may in rare cases pass from the primary lesion into the body generally.

(2) The chronic infections. The only difference between the bacterial effects here and those in the acute infections is in the time which elapses after infection before tissue-changes and general effects are manifest. Usually the vascular changes present in acute inflammations are to a large degree absent, and the cellular degenerations of a rapid kind, such as acute necrosis, karyorrhexis, are replaced by more slowly developing interferences with vitality, such as fatty degeneration, hyaline degeneration, and so forth. The reactive changes of the hæmic leucocytes may often not be marked in the early stages, whereas the proliferation of cells more related to the fixed tissues, *e.g.* the plasma-cells, may early occur; sometimes an actual formation of new connective-tissue takes place. The typical representatives of the chronic infections are the so-called infective granulomata, tuberculosis, actinomycosis, Madura foot, leprosy, glanders. The chief site of multiplication of the causal bacteria is in the lesions, especially in their central parts. From the original site of infection the bacteria may spread by the lymphatics or blood-stream and produce fresh foci. The course of the infection can often be traced after death by the relative degrees of advance, especially in degenerative processes manifested in different foci. In the chronic infections general changes, here again of a slowly developing character, such as fatty and lardaceous, may occur. The line of demarcation between acute and chronic infections is artificial. In several cases an acute infection may be set up by an organism usually acting slowly. Thus in glanders in man, an infection characterised by acute inflammation may occur either as the terminal phase of a chronic condition or in an acute form from the outset.

(3) The bacterial intoxications. The usually quoted examples of these in man are diphtheria and tetanus. In both diseases the main effects are brought about by the absorption from a focus of bacterial growth

of soluble toxins with a specific action. The area of bacterial invasion is strictly local, and the micro-organisms do not gain access to the body tissues under any natural conditions. Though the chief effects of the diphtheria bacillus are due to toxic action, there is also a local inflammatory condition which is fundamentally of an ordinary character. To this class of disease cholera, as it occurs in man, probably belongs, since the bacteria are confined to the intestine and appear to produce their effects by toxic action. It is also probable that the main action of the influenza bacillus is toxic, though of course there is a local reaction in the respiratory passages.

III. Immunity

Introductory. — On investigating the properties of pathogenetic bacteria it very soon becomes apparent that there are no bacteria which in all circumstances will produce disease in all species of animals or even in all individuals of a species. This phenomenon occurs quite apart from the vital activity of the germ. When an animal species is infected with an organism but does not develop disease, that species is said to shew immunity against the organism. Immunity of individuals belonging to an otherwise susceptible species is also exhibited. It must further be recognised that there are degrees of immunity, both in individuals and species. In fact, we shall later have to consider whether such a condition as an absolute immunity exists.

It is customary to speak of immunity as it is found in ordinary conditions as natural or acquired. The idea of a *natural* immunity arises from a consideration of the epizöotic incidence of infectious disease. Thus, while some diseases such as anthrax, glanders, and tuberculosis, affect many species of animals, other infections are more limited in their distribution. Cholera and typhoid fever, found in man, do not affect the lower animals; and foot-and-mouth disease and swine fever are found among species of domestic animals, but not in man. Again, the existence of an *acquired* immunity has long been known. Immunity is ordinarily acquired as the result of a susceptible individual passing through an attack of a disease. As we shall see, there is reason to believe that in many cases recovery from infection depends on an individual developing certain qualities in his body during the course of his illness. These qualities determine the cessation of the pathogenetic action of the bacteria and also result in the death of these bacteria. Thus, in many cases, it is no doubt true that at the close of an illness an individual is immune. The duration of the acquired immunity, however, probably varies; in some cases, as in streptococcus infection, pneumonia, influenza, and in some individuals in diphtheria and measles, the immunity is short-lived, and it is questionable whether in some cases it may not be succeeded by a greater susceptibility. In other diseases, as scarlet fever, smallpox, and enteric fever, immunity usually endures for life. In

certain cases the apparent persistence of immunity may be complicated by the natural decrease of susceptibility which occurs in advancing age; but that this may not be the sole cause is shewn by the experience that in the case of some diseases, such as smallpox and typhus fever, an unprotected individual manifests susceptibility till at any rate very late in life.

The interest of medical science in the subject may be said to date from the introduction into England, about 1720, by Lady Mary Montagu, of the practice of inoculating healthy individuals with exudations from smallpox pustules. Edward Jenner's thoroughly scientific investigation in 1798 of the protective power against smallpox in man produced by a mild non-infectious attack of vaccinia forms the starting-point of all recent work on the subject. Jenner's papers appeared in the closing years of the eighteenth century, but it was not till eighty years later that any further advance was made. The proof of the bacterial origin of many infectious conditions cleared the way for more precise research, and it was Pasteur who now broke new ground. In investigating an epidemic disease of fowls—known as fowl cholera—he found that if animals were inoculated with attenuated cultures and subsequently with ordinary cultures they no longer succumbed to the disease—they were immune. This work, published in 1880, forms the starting-point of all subsequent investigation.

The subsequent historical landmarks are the vaccination against anthrax, also discovered by Pasteur, the principle of which was immunisation by cultures weakened and rendered asporogenous by growth at 42° C.; the elaboration by Pasteur of the protective inoculation against the unknown cause of hydrophobia, in which the virus existing in the spinal cord is attenuated by drying; and the introduction by Behring of the method of neutralising the poison of diphtheria by an antitoxic serum.

Immunity, Active and Passive.—There is no subject in medical science which presents greater difficulty than the problem of immunity. This is explained partly by the inherent complexity of the matters at issue, partly by the lack of sufficient pains in defining clearly the relationships of any particular line of investigation to general principles, and partly because the problems have been attacked from so many sides that the relations of the particular to the general have often not been evident. Further complication has arisen because investigations had not proceeded very far before facts with most important therapeutic applications emerged. It was found in certain cases, when an animal acquired immunity against a disease manifestation by passing through an infection or infections with the causal agent, that the acquisition of immunity was associated with the development of new qualities in its blood-serum. If this serum were introduced into the body of another susceptible animal, the latter shewed a loss of susceptibility to infection. In such circumstances the immunity of the first animal is spoken of as *active*, or sometimes as *isopathic*, immunity, because it is by some process going on in the animal's

own body that the immunity is developed; the immunity in the second case is called *passive* immunity, because the animal does not depend for its insusceptibility to infection on the activity of its own tissues. The therapeutic application of passive immunity lay in the discovery that even after infection had taken place the introduction of serum from an immune animal may prevent the fatal conclusion of the illness which otherwise might be expected. For these therapeutic applications of the results of immunity investigations it was necessary, for reasons that will be explained later, to endow animals with an immunity of an extraordinary and excessive degree. Study of the phenomena of such excessive immunisations has not always resulted in a proper appreciation of the true relationships existing between this abnormal immunity, as it might be called—of an immunity outside the personal requirements of the immunised animal—and the normal immunity such as protects an animal for the whole or a part of the natural term of its own life.

The Problems of Immunity.—In connexion with the essential points requiring explanation under the heading of immunity the following considerations arise. In a very large number of cases in which bacteria gain a footing in the animal body and cause changes in it, their growth is not unlimited but comes to an end; recovery from bacterial disease is, in fact, a very common occurrence. In almost no case does it happen that when one bacterial cell gains entrance to the body death will invariably follow, though occasionally, as in some strains of streptococci obtained by Marmorek (214), this appears to have occurred. Usually bacteria flourish in the bodily tissues for a time and then die. In artificial cultures, where the same phenomenon occurs, a bacterium hardly ever uses up all the available food material, but secretes poisons which ultimately destroy its own vitality. If the filtrate of a fluid medium on which an organism has been allowed to grow for a short time be inoculated with the same organism very often no new growth occurs. Attempts have been made by Emmerich and Löw (117) to explain some of the phenomena of immunity on the supposition that a similar destruction of bacteria by their own products may occur in the animal body. Not only, however, is the evidence for this view insufficient, as has been shewn by Dr. Petrie (269), but there is overwhelming evidence that the reason for the cessation of bacterial activity in the animal body is to be found in the counter-activities of the tissue-cells. The first problem of immunity to be dealt with concerns the phenomena of recovery from bacterial disease. These phenomena are exceedingly complicated. As already pointed out, bacteria chiefly act as disease-producing agents in virtue of the production of poisons. Now it is evident that the effects of bacterial action might be combated either by the body neutralising the poisons produced or by its killing the bacteria that manufacture these poisons, and thus cutting off the source of the danger. As a matter of fact, the body can provide substances capable of neutralising some of the poisons produced by bacteria. What relative part the two capacities play in recovery in any particular case is a very difficult question. The

next problem that presents itself is the explanation of the fact that when an animal passes successfully through a bacterial attack it acquires a capacity of partially or entirely resisting future invasion by the bacteria involved, so that, for instance, when the same number of bacteria which formerly caused disease are introduced into its body no pathological effects result. As a subsidiary problem here we have to explain the mechanism involved when the serum of an actively immunised animal protects another animal against infection. Finally, we must consider those cases in which an animal seems naturally to possess a degree of immunity that another animal has to acquire, and also whether such natural immunity is ever absolute. The main problems for consideration, therefore, are:—

(1) The phenomena of recovery from disease.
(2) The phenomena of acquired immunity.
  (*a*) Of active acquired immunity.
  (*b*) Of passive acquired immunity.
(3) The phenomena of natural immunity.

Underlying these problems are the very important questions relating to the essential nature of bacterial virulence and to the mechanism of susceptibility to disease.

In discussing these problems we shall, first of all, consider in detail the capacity of the body to form substances antagonistic to the action of certain bacterial poisons; secondly, the capacity of the body to form substances possessed of the power of destroying bacteria; and, lastly, the problem of the relation of these capacities to the activities of bodily cells which can be microscopically demonstrated. Such a review will cover practically all the problems of immunity enunciated.

The Phenomenon of Antitoxin-Formation

Our thesis here is as follows:—*In the case of many bacterial poisons if the toxin be absorbed by the body of an animal, and if after a time the animal be bled, the serum separating from its blood is found to have the capacity of neutralising the poison used.* Such a serum is called the antitoxin for the particular toxin under consideration. The bacterial toxins against which antitoxins can be produced belong chiefly, if not entirely, to the diphtheria group of toxins, but the inherent power of the animal body to produce antitoxins has numerous and far-reaching possibilities. Not only can poisons stimulate the production of antidotes, but certain other substances, such as some ferments, when injected into animals stimulate the production of serums which antagonise their action. The study of antitoxin-production by the diphtheria group of bacterial toxins constitutes a comparatively simple problem, because the poisons are soluble in simple watery solution, and thus the investigator can easily obtain them apart from living bacterial protoplasm. We shall see reason to believe, however, that even their apparently purest form is still probably only a mixture of different substances. The poisons which

have been most studied are those produced by the diphtheria and tetanus bacilli.

Development of Knowledge regarding Antitoxins.—Many facts regarding immunity against soluble bacterial toxins have long been known. The pioneers of investigation here were Foà and Bonome (124), who, in 1889, shewed that a poison isolated by filtration from a pathogenetic variety of the *Proteus vulgaris* (one of the ordinary putrefactive organisms) produced an antitoxic serum. There was considerable controversy at this time regarding the method by which living bacteria were destroyed in an animal immunised against the action of these bacteria. The view that this occurred solely in the serum of the animal had, as a further development, supposed the presence in the serum of poisons fatal to the life of the bacteria. The evidence in regard to this conception was, however, of a very contradictory character, and Behring, both alone (19) and in conjunction with Wernicke (24), turned to the study of the simpler problem of how immunity arose against the diphtheria and tetanus bacilli. Behring and Kitasato, continuing Behring's previous work on the actions of antiseptic chemical substances, shewed that the injection of iodine terchloride had a definite effect in preventing death in an animal (*e.g.* rabbit) after infection with tetanus bacilli or toxin; and Kitasato found that in such an animal a tolerance to the poison was established—in short, the animal was immune. He further shewed that if after repeated toxin injections a little of the blood-serum of the animal were injected into a second animal, this latter was protected against an otherwise fatal infection with tetanus. Similar results were obtained by Tizzoni and Cattani (324), and Behring and Wernicke found that guinea-pigs infected with diphtheria bacilli and treated with iodine terchloride could by procedures similar to those of Kitasato be rendered immune to diphtherial infection. They further shewed that it was immaterial whether the animals were infected with cultures or toxin and then treated with the iodine compound, or the latter was allowed to act on the morbific agent outside the body previous to its injection. They shewed, also, that in those animals immunised against diphtheria the serum possessed the property of protecting other unimmunised animals against infection which otherwise would have proved fatal. It was also found that injection of the serum after inoculation, and even after the onset of symptoms of the disease, might avert a fatal result. In such circumstances the longer the time which had elapsed between the infection and the application of the serum the greater was the dose of the latter necessary for a successful issue. This work is the foundation of the brilliant results obtained in the therapeutics of diphtheria during recent years. The fundamental deduction made from the facts observed—a deduction which is still unshaken—is that in the blood-serum of an animal immunised against a bacterial toxin there appears a substance having the power of antagonising the toxin. The serum containing this substance is, as we have said, known as antitoxin. The appearance of this antitoxic quality in an animal's serum was

stated by Behring to be the cause of the animal's immunity, and this view is often put forward. Whether this is or is not justified will be discussed later. There will not be any loss in clearness of conception if we content ourselves here with the simple assertion that an antitoxic substance appears in the serum of an immunised animal. This antitoxic substance, further, is capable of neutralising both inside and outside the body the toxin which caused its formation. It may also be stated here that an antitoxin is only capable of neutralising the toxin which stimulated its production.

The obtaining of Therapeutic Serums.—The fact that enormous doses of antitoxin must often be given has made it necessary that serums of extraordinary antitoxic power should be prepared, in order that the amount of antitoxin to be used should be contained in an amount of serum which it is safe to inject. Such serums are obtained by the abnormal immunisations to which reference has already been made. These immunisations are outside the requirements of the animal immunised, and are correlated to the necessities of another animal.

An idea of the procedures employed can best be obtained by the description of the immunisation of a horse as given by Roux (292).

1st day. Subcutaneous injection of ·25 c.c. diphtheria toxin exposed for a short time to the action of ·025 c.c. Gram's solution of iodine.

2nd day. Subcutaneous injection of 5 c.c. toxin exposed to ·05 c.c. of iodine solution.

4th, 6th, 8th days. Subcutaneous injection of 1 c.c. toxin exposed to ·1 c.c. of iodine solution.

17th day.	Subcutaneous injection of	·25 c.c.	crude toxin.
22nd day.	,,	1	,,
23rd day.	,,	2	,,
25th day.	,,	3	,,
28th day.	,,	5	,,
30th, 32nd, 34th days.	Subcutaneous injection of	5 c.c.	crude toxin.
39th, 41st days.	,,	10	,,
43rd, 46th, 48th, 50th days.	,,	30	,,
53rd day.	,,	60	,,
57th, 63rd, 65th, 67th days.	,,	60	,,
72nd day.	,,	90	,,
80th day.	,,	250	,,

The toxin used was such that 1 c.c. killed a guinea-pig of 500 grammes in forty-eight hours. This horse yielded a serum of by no means great antitoxic power as compared with others that have been obtained.

It is customary to use large animals, such as the horse, in the immunisation procedures for the purposes of obtaining therapeutic serums, as of course large quantities of serum can thus be readily obtained. All horses do not react in the same way to toxins, and sometimes animals are met with which, while tolerating large doses of toxin, do not yield a highly antitoxic serum. Great judgment and experience are always required in

determining the size of successive doses of the toxin. Not only may the animal be killed by too large a dose of toxin, but too marked a reaction may interrupt the course of the antitoxin development. During the immunisation the antitoxic strength of the serum is tested by the removal from time to time of small quantities of blood. When a sufficiently high antitoxic value has been attained, the animal is bled to the limits of safety from the jugular vein, and the serum is separated under aseptic precautions. The animal is allowed a few months to recover, and the immunisation process may be repeated again and again. The course of the development of antitoxin in an animal during a period of toxin injection has been studied by several observers, particularly by Salamonsen and Madsen (301). Generally speaking, it may be said that a toxin injection, or a series of toxin injections, cause in the course of a few days a rapid rise in the amount of antitoxin in the serum, which is succeeded by a very gradual fall. If during the rise a fresh toxin injection be practised there is often a sudden drop in the antitoxic value of the serum. This is not entirely explained by supposing that the toxin injected enters into chemical combination with the antitoxin present in the blood and thus causes the latter to appear weak in antitoxic content; it can be shewn by exact measurements that this does not account for the drop, which is therefore probably due to interference with the production of antitoxin. The phenomenon is sometimes referred to as the occurrence of a *negative phase.* After the sudden drop the antitoxic value of the serum often rises rapidly to a level higher than the previous maximum. Similar reactions may recur with successive injections, but in any animal the capacity for antitoxin-production is limited, and a time comes when fresh injection of toxin is either not followed by a rise in the antitoxic value of the serum, or may be followed by a tendency to a rapid fall. It is just before this point is reached that the animal ought to be bled, and it is in the recognition of the time at which the greatest result is obtainable that the skill of the immuniser lies. With regard to the duration of an antitoxic value in the serum of an actively immunised animal, an important point has been raised. It has been stated that the duration is much longer than is the case when an animal is merely passively immunised. Behring (17) is of opinion that what has been observed in such cases is explained by the fact that for the passive immunisations in question serum from another animal species has been employed. If horse-antitoxin be injected into a guinea-pig or rabbit, the antitoxic value of the body-fluids of the latter rapidly falls, but if horse-antitoxin be injected into a horse the disappearance of the antitoxin is not much more rapid than if the animal by active immunisation had attained the same antitoxic value in its serum. It has been suggested, partly from the last observation, that better therapeutic results in man might be obtained by using serum derived from the immunisation of apes, but so far as we know this suggestion has not up till now been acted on (*vide* Behring and Kitashima (21)).

Since the introduction of the serum treatment for diphtheria and

tetanus comparatively little change has taken place in the technique employed in obtaining the serum. Different workers have varied the details of the process of immunisation. Sometimes this has been commenced by the injection of toxin modified by iodine terchloride, sometimes by the iodine solution used by Roux (292), sometimes no modification has been employed, and small non-lethal doses of weak toxin have been employed in the early stages. As time has gone on, however, great precision has been attained in the measurement of the strength of toxins used and the antitoxins produced. The standards are artificial, for neither toxin nor antitoxin can be obtained in a pure condition, and thus a gravimetric system cannot be adopted. These substances can only be standardised in terms of their toxicological or pharmacological effects.

The Standardisation of Antitoxins.—The main use of standardisation methods is in relation to therapeutics, but as they are necessary for exact scientific work they must be described here. The minimal lethal dose, which has already been referred to (p. 36), is a fundamental factor, and, as we have pointed out, its determination rests to a certain extent on an artificial basis. In the case of diphtheria toxin the definition adopted by Ehrlich (104, 106, 115) is generally acted on. The M.L.D. is the amount of the crude toxin which will kill a guinea-pig of 250 grammes on the fourth day. In the case of tetanus a similar definition works very well. Sometimes it is reckoned in terms of white mice, and then the amount which kills a mouse in about five days is employed. The strength of an antitoxin is measured in terms of the M.L.D. The most widely adopted method is that of Ehrlich, who defines the "immunity unit" as the amount of serum which, when mixed *in vitro* with 100 M.L.D. of toxin and injected into a guinea-pig of 250 grammes, will prevent death from taking place during the succeeding four days. When this amount of antitoxin exists in 1 c.c. of serum the latter is called a normal serum. In the case of diphtheria the injection is made immediately after the act of mixing, but in that of tetanus the mixture is left at 37° C. for three-quarters of an hour before being used. We shall see that there is little doubt that the antagonism between toxin and antitoxin is a chemical one, and in Ehrlich's view the affinity between the two substances is much stronger in the case of diphtheria than in that of tetanus. Behring (22) has adopted a different method of calculation, though the ultimate value of an "immunity unit" is identical. The numerical value of a serum is expressed by him in terms of the body-weight of the experimental animal. Thus a serum which, when injected into a guinea-pig in the proportion of 1 : 10,000 of the animal's body-weight, protects it against the fatal action of 100 M.L.D. is said to have a value of 1 : 100 × 10,000, *i.e.* of 1 : 1,000,000; this symbolism is also adopted by Roux. In what follows Ehrlich's nomenclature will be mainly employed, and the two points here to be kept in view are the conceptions of the "minimum lethal dose" and of the "immunity unit." The degree of immunisation obtained in animals treated for the manufacture of therapeutic sera may be judged of

by the fact that it is not uncommon to have a serum which in 1 c.c. contains 1000 "immunity units." By far the greatest amount of work done with regard to immunisation against specific toxins has been in connexion with the diphtheria and tetanus toxins.

The Antivenenes.—The most extended observations with regard to other antitoxins are, however, those which deal with snake-poisons. Here the chief workers have been Calmette (64), Fraser (127), C. J. Martin (220), Lamb (174*a*, 175), Tidswell, Flexner and Noguchi (123). It has been found that the same general principles are applicable in producing immunity here, and the antitoxic principles have been named by Sir T. Fraser "antivenenes." Certain special difficulties have, however, been encountered. Immunity has been produced both in small animals, such as rabbits, and in large animals, such as horses, against a great variety of snake-poisons; of these the chief have been the cobra (Calmette, Lamb, Fraser), the rattlesnake (Fraser, Flexner and Noguchi), the Australian snake *Hoplocephalus curtus* (Tidswell), *Diamantena* (Fraser). In some cases the immunisation has been commenced with small doses of the venom, in other cases the latter has been first weakened by heating, in others the weakening effect has been produced by chemical agents, as by hydrochloric acid (Flexner and Noguchi). The difficulties in the way of immunisation in some cases lie in the complicated composition of snake-venoms, to which allusion has been made when dealing with the subject. Thus, to take the rattlesnake-poison, while it apparently is quite easy to influence the neurotoxic and hæmolytic elements, that which produces hæmorrhage and necrosis (hæmorrhagin) is difficult to affect, and may interfere in an immunisation by making it impossible to inject large doses of the venom, even after immunisation against the other two elements has been considerably manifested. Flexner and Noguchi have, however, in this particular case overcome the difficulty by the use of the hydrochloric acid method. According to Major Lamb different horses react differently. An extremely important point is that the serum never attains such a high order of potency as is the case with diphtheria and tetanus. In the case of cobra poison a strong serum is one in which 1 c.c. neutralises the effects of 1 milligramme of the poison. As, for small animals (dog, rabbit, guinea-pig, monkey), the M.L.D. runs from a quarter to half a milligramme per kilo., it is evident that such a serum is relatively weak. The serums prepared, however, all have the power of neutralising *in vitro* the poison producing them, and when injected into an animal previous to the injection of the venom, they prevent the action of the latter. They may also, if injected beforehand, prevent a fatal effect from the actual bite of the snake, but here a difficulty arises in that, in the case of such a snake as the cobra, an amount of poison many times exceeding the M.L.D. may be ejected from the poison-gland. A point of great interest in connexion with snake-venoms is this. Is an antivenene produced by the venom of one snake capable of neutralising that venom only, or will it also neutralise the venoms of other snakes? Sir T. Fraser held the opinion, based on his own experiments,

that an antivenene was not strictly specific towards its own venom. Calmette has always held this opinion, and has recently been supported by Roger. On the other hand, Drs. C. J. Martin, Tidswell, and Major Lamb have held that an antivenene is either absolutely or almost entirely specific. The evidence is in favour of the existence of a very marked, though not quite absolute specificity. The essential difficulties in the problem of specificity lie in the different compositions of different venoms already alluded to, and, further, in the fact that the different components produce different effects. It is evident that snake-antivenene might be a correspondingly complex body, and taking for granted that the neutralisation of the constituents of the venoms by the constituents of the antivenenes is of a chemical nature, it follows that an antivenene produced by the injection of the venom of one snake might be poor in one or more constituents required for the proper neutralisation of the venom of another snake. The problem, however, may not be so simple, and another possibility must be faced, namely, that a constituent of a venom A which has toxic effects identical with a constituent of a venom B, may yet be only capable of neutralisation by a constituent of an antivenene produced by the injection of venom A. One final point may be mentioned in regard to these snake-poisons, namely, that the constituents of venoms which in their action in producing antitoxins must closely resemble such toxins as those of diphtheria and tetanus are the neurotoxic constituents—those which act on the nervous system. In the cases of some other constituents the mode of action is extremely complex, as will be seen later. [*Vide* art. "Snake-poison and Snake-bite" in volume on "Tropical Diseases."]

We thus see that against several specific toxins, both of bacterial and animal origin, immunity can be produced, that this immunity can be pushed to very high degrees, that, with this development of immunity, bodies antagonistic to the toxins, and therefore called antitoxins, appear in the animal's serum, and that the antitoxic strength of an immunised animal's serum may be made to exceed greatly any standard required for the protection of that animal against ordinary infection.

Chemical and Physical Properties of Antitoxins.—With regard to the chemical nature of the antitoxic principle in the blood nothing is known. It can be precipitated by alcohol, ammonium sulphate, and the ordinary precipitants of the higher proteids, and according to some observations (Freund and Sternberg, Brieger and Cohn) the antitoxins to diphtheria and tetanus are precipitable with the globulins of the serum containing them. Their molecular complexity appears to be of an order higher than that of the albumoses. The evidence on which this view rests is adduced by Dr. C. J. Martin (218, 221). This observer has used for the filtration of albuminous substances a porcelain filter with its pores filled with gelatin. There is thus formed what in reality is a strongly supported dialysing membrane, and through it albumoses and peptones will pass, while the higher albumins will not pass. It is found that antitoxins are retained by such a filter, and from this Dr. Martin

concludes that their molecules are larger than those of albumoses. This is also borne out by the fact that toxin is much more rapidly absorbed from the subcutaneous tissues of an animal than is antitoxin. The question, however, has been raised whether antitoxins may not be bodies simply associated with the globulins of a serum; Brieger and Boer (46) have stated that by means of zinc sulphate they have precipitated from diphtheria antitoxin a non-proteid substance which exhibited the antitoxic properties of the serum. It is evident that chemistry can as yet teach us little concerning the nature of these substances. Certain physical properties may be mentioned. The antitoxic quality of a liquid serum is destroyed by a short boiling, and a more prolonged exposure to temperatures of from 60°-70° C. has the same effect. In the dry condition a serum can withstand a temperature of 140° C. for a quarter of an hour without injury. Dry serums exposed to air and to ordinary atmospheric moisture lose their potency, and to prevent this Ehrlich stores his antitoxins in double-bulbed tubes, the serum being placed in one and anhydrous phosphoric acid in the other; the tube is then exhausted by a mercurial pump, sealed, and kept in the dark; in such a state the antitoxin apparently maintains its potency unchanged for a very long time.

The Nature of the Antagonism between Toxin and Antitoxin.—We must now consider the probable nature of the antagonism existing between an antitoxin and its corresponding toxin, in virtue of which no effects are produced when a mixture of the two substances in suitable proportions is injected into an animal susceptible to the toxin under investigation. Evidently there are three possibilities : in the first place the antitoxin might break up the toxin, and thus destroy its harmful action; secondly, it might combine with it to form a neutral substance having no effect on the tissues; thirdly, it might act not in a chemical manner such as is entailed in the first two possibilities but in a physiological manner—in other words, while the toxin might have one effect the antitoxin might have an opposite effect, and thus neutralise the toxic action. From want of evidence the first possibility has never been considered, and only the second and third hypotheses have been discussed in the light of available facts.

Evidence adduced for the Antagonism being Physiological.—The three experiments brought forward in support of such a view taken in order of importance are those of Calmette, Buchner, and Wassermann. Calmette (64*a*), working with a snake-venom, found that it could withstand without injury a temperature which destroyed the neutralising properties of its antivenene. He determined the quantity of the antivenene which neutralised a given amount of venom, so that when the two substances were injected in these proportions into an animal no result followed. He took such a mixture neutral *in vitro* and heated it to the point that would destroy the capacity of the antivenene without affecting the venom; he found that, on injecting the mixture into an animal, death occurred just as if untreated venom had been used. From

this he inferred that in the mixture of venom and antivenene no actual combination had occurred, that the two substances existed side by side, and that the neutralising action took place within the body of the animal into which they were injected. Omitting the possible criticisim that there exists in the toxin-antitoxin mixture a chemically unstable union easily resolvable by heat with destruction of one of the constituents—an occurrence which could be paralleled from known chemical facts—we pass to the criticism of Drs. C. J. Martin and Cherry (221), based on an amplification of Calmette's experiment. These observers found that the longer the venom and antivenene were left in contact before the heating of the mixture, the less evidence was there that venom was left free after heating, and at last a point was reached when the heated mixture no longer manifested any toxic properties whatever. There was thus abundant evidence of an interaction *in vitro* between the venom and the antivenene. It cannot therefore be urged that in reality Calmette's experiment legitimately carries the interpretation originally put on it by its author. Next with regard to Buchner's work (50*a*). This observer took a tetanus toxin of which ·0001 gramme killed white mice in from two to three days. This dose had little or no effect on guinea-pigs averaging 344 grammes in weight. Of this toxin ·014 gramme was mixed with ·00135 gramme of tetanus antitoxin, and injected into each of a series of 23 mice and of 23 guinea-pigs. It is usually stated that the mixture was neutral for the mice, but produced pathogenetic effects on the guinea-pigs. But this was not the case, for among the mice 9 only remained unaffected, 11 shewed slight chronic tetanus, 3 died; of the guinea-pigs 3 remained intact, 12 shewed chronic tetanus, and 8 died. The inference originally drawn by Buchner was that a mixture of toxin and antitoxin, neutral or nearly neutral, for one animal species was not necessarily neutral or nearly neutral for another, and that therefore the neutralisation-phenomenon was probably not of the nature of an ordinary chemical neutralisation. We consider that it is difficult to say whether such a conclusion is or is not justified by the data. The experiment was performed before the use of the modern accurate methods of measuring toxic and antitoxic capacities had been elaborated. A more important point is that no mention is made of the duration of the exposure *in vitro* of the two antagonistic solutions, nor is it stated if the duration was the same in the two series of experiments. In view of the fact that, as we stated, there is evidence that toxin is absorbed more easily than antitoxin from the subcutaneous tissues, it is obvious that if a mixture containing these substances, not in combination, be injected, the poison gets to work at a greater rate than the antidote. Again, as will be shewn later, even if a mixture of the two substances in a state of combination be introduced, dissociation might take place, and this would probably occur to a greater extent in the body of a very susceptible animal than in one of less susceptibility. The real meaning of susceptibility to a toxin will be discussed later. The third experi-

ment on which the physiological antagonism of toxin and antitoxin is supposed to rest is that of Wassermann (346*a*). This observer states that a neutral mixture of the toxin of *B. pyocyaneus* with its antitoxin, when heated to 100° C. and injected into a guinea-pig, proves to be no longer neutral. No statement, however, is made regarding the effects of different lengths of exposure *in vitro* before the treating, and it may further be pointed out that as Wassermann's so-called soluble toxin is in reality a bouillon culture killed by being shaken up with toluol, it certainly will contain the bodies of the bacteria and the poisonous proteins they contain. In fact, it is doubtful if the *B. pyocyaneus* forms any soluble toxins of the nature of these formed by the *B. diphtheriæ* or the *B. tetani*. There were evidently several peculiar points regarding the organism, as, for instance, the fact that immunisation of the living bacterium did not originate immunity against the "toxin," and the significance of Wassermann's observation on the heating of the "toxin-" antitoxin mixtures would require further investigation.

Evidence adduced for the Chemical Nature of the Antagonism.—Inquiry must be made whether any evidence exists in support of the view that in the antagonism between toxins and antitoxins a chemical union really takes place between the two substances. Early in the discussion of the subject Ehrlich pointed out that the relations between the two substances presented many similarities to what is observed in chemical reactions. Thus, if a supposed neutral mixture of diphtheria toxin and antitoxin were exposed to a higher temperature than that adopted for the experiments by which the neutralisation had been determined, neutralisation-phenomena appeared earlier, *i.e.* the union was hastened by heat. There was a corresponding delay with the application of cold. Further, union took place more rapidly when the solutions were strong than when they were weak. There is, however, other and more particular evidence that toxins and antitoxins enter into chemical combination with one another. Allusion has already been made to the experiments from which Drs. C. J. Martin and Cherry deduce that the antitoxin molecule is of larger size than the toxin molecule, in that the latter can pass through a strongly supported gelatin film, while the former cannot. These observers, working with diphtheria toxin and antitoxin, made the following further observations. They placed in the filter a mixture of the poison and antipoison some considerable time after the mixture had been made, and applied great pressure to it by means of compressed carbonic acid gas. Anything present that was capable of passing through the gelatin was thus placed in a position to be driven through. It was found that though diphtheria toxin by itself could easily pass through such a filter, the fluid coming through from a mixture previously allowed to stand for a time was not toxic to animals. From this it was deduced that if sufficient time be allowed the diphtheria toxin gradually *in vitro* enters into combination with the antitoxin. Dr. C. J. Martin (219) also makes a similar deduction regarding the venene-antivenene experiments already cited in connexion with Calmette's contention.

But there is evidence of another kind that the toxin-antitoxin neutralisation is based on a chemical union between the two substances and not on physiological antagonisms, in that the neutralisation-phenomena can be observed in circumstances where the possibility of physiological action on the part of toxin is excluded. Several examples of such a process can be quoted. From the castor-oil bean, as we have seen, a soluble poison can be very readily extracted. By the ordinary methods immunisation can be produced against the toxin, and there appears in the serum of the immune animal an antiricin with the usual antagonistic properties. Ehrlich shewed that *in vitro* ricin has the effect of causing red blood-corpuscles suspended in saline solution, in the proportion of five parts of blood to ninety-five of the diluent, to become massed together in clumps, which fall to the bottom of the test-tube containing them. He shewed that antiricin had the effect of protecting corpuscles against the clumping effect. Here evidently there could be no physiological effect produced, at least if the ordinary view as to the passive character of the protoplasm of the red blood-cell be accepted. Again, Drs. Stephens and Myers (319) discovered similar facts regarding the effects of cobra-poison on red blood-corpuscles. As has been pointed out, this venom causes hæmolysis or the solution of the red cells. These observers found that *in vitro* red blood-corpuscles could be protected against hæmolysis by the presence of antivenene. Kossel confirmed this in the case of the hæmolytic action of the serum of the eel, which is toxic for the rabbit, and owes part at least of its poisonous action to the capacity it possesses of dissolving the red corpuscles of the animal. Rabbits can be immunised against the poisonous action, and here, again, the serum possesses antitoxic properties which are active, in that *in vitro* they protect red cells against the toxin. These two cases manifestly stand on the same footing as Ehrlich's results on the agglutinating action of ricin, in that cells incapable of physiological response do not undergo a specific change when the active body is in the presence of a neutral substance. As the presence of a depressing effect neutralised by a stimulating effect is here out of the question, the deduction is legitimate that the antagonism between the two substances is of a chemical nature. But still more convincing evidence in favour of this conclusion is found in certain results of Kanthack (152) and of Morgenroth (244). The former, who indeed was the first to bring forward any evidence of chemical antagonism in the toxin-antitoxin reaction, shewed that the power of cobra-venom to prevent the coagulation of the blood could be neutralised by cobra-antivenene. Morgenroth investigated the phenomena occurring in the goat when ordinary rennet ferment was injected after the manner of an immunisation. The goat's serum was found after a time to have the capacity of preventing curdling of cow's milk by rennet. In this experiment it should be noted that we are dealing with the action of a substance on totally inert material, namely, the soluble albumins of the milk, and that, since physiological action and reaction are out of the question, the antagonism of the rennet and

antirennet must be chemical. The only objection that can apparently be urged is that toxins may differ from ordinary digestive ferments. But toxins and ferments have this at least in common, that they belong to the very special class of bodies against which specific antibodies can be produced in the animal organism, and it is in the highest degree probable that, as the production of the antibodies results from the operation of the same laws, the same laws also govern the antagonism in the two cases.

We may sum up here by saying that evidence of a physiological antagonism between the group of toxins and the group of antitoxins is wanting, and from what we know there can be very little doubt that neutralisation phenomena are due to a chemical reaction between the opposing substances.

The Ultimate Nature of the Toxin-Antitoxin Reaction.—We have seen that the methods of ordinary chemistry can as yet throw no light on the true nature either of toxins or of antitoxins. Thus, while by indirect evidence we have arrived at the conclusion that the interactions of the two substances are of a chemical nature, we cannot look to the chemist for information as to the real nature of what takes place. In these circumstances Ehrlich (104) has advanced a hypothesis based on certain relations observed between crude toxins[1] and crude antitoxins. The essence of his hypothesis is that certain experiments with toxin-antitoxin mixtures in animals can best be explained by supposing that the two substances possess certain chemical properties. This method of chemical analysis is certainly novel, but so cogent are the arguments adduced by its author that though these arguments are of a highly theoretical character, Ehrlich's views may be said at present to dominate the whole field of immunity inquiry. The hypothesis touches the problems at issue at many points. Of these the chief have reference to the nature of toxins, the nature of bactericidal action, and the nature and origin of antitoxins. In its application to the nature of the toxin-antitoxin reaction, the hypothesis involves the consideration of certain points bearing on the probable ultimate constitution of the toxin molecule.

The Ehrlich Phenomenon.—All Ehrlich's work is based on his researches with diphtheria toxin, but there is evidence that the fundamental deductions made are applicable to other toxins of the same kind. His hypothesis starts from, and in its development rests on, an observed fact, of the existence of which there can be no doubt. This is the so-called "Ehrlich phenomenon." This phenomenon may be stated in its simplest form as follows:—If a mixture of crude diphtheria toxin and diphtheria antitoxin known to be exactly neutral

[1] We shall now have frequent occasion to distinguish between *crude toxin* (*i.e.* the toxic filtrate of a bouillon bacterial culture) and the *true toxin* it contains, and to which its poisonous properties are due. It may be also convenient to speak of crude antitoxin (*i.e.* the serum of an immune animal) and the true antitoxin which it contains, and to which it owes its neutralising action. Here, however, as we shall find, an antithetical phraseology is not so essential to clear understanding.

be taken, and there be added to it one minimal lethal dose of crude toxin, and the whole be then injected into an animal, we should expect death to follow; but this practically never occurs. It will be well to detail the investigations which led to this discovery. In the case of each of a number of samples of crude diphtheria toxin derived from the growth of different races of diphtheria bacilli, the following steps were taken. First the minimal lethal dose of the crude toxin was determined. To a series of moieties of antidiphtheric serum, each containing one immunity unit (*vide* p. 54), different and increasing amounts of crude toxin were added, and each mixture was injected into a guinea-pig. Following on these injections some animals (those which received mixtures containing the smaller amounts of crude toxin) remained in perfect health, some (those receiving higher amounts) suffered from the slighter symptoms of diphtheric poisoning (*e.g.* paralyses) and recovered, some manifested symptoms and died after an illness of more than five days' duration, some died of an acute illness of five days' duration characterised by fever, cardiac failure, and so forth, and some (those which received mixtures containing the highest amount of crude toxin) might die from similar acute effects in an even shorter time. In analysing such a series of results Ehrlich directs special attention to the composition of two of the toxin-antitoxin mixtures. In the first place there is the mixture which, in reference to the rising series of amounts of crude toxin, is just below the mixture causing the slightest symptoms of disease; this mixture is non-pathogenetic, since complete neutralisation of the toxin by the antitoxin has taken place. In mixtures containing smaller multiples there is excess of antitoxin; in that containing the next higher multiple there is a slight amount of unneutralised toxin, and, as a result, slight symptoms follow. In such a series as this, this upper limit of complete neutralisation is denominated in Ehrlich's terminology, "*Limes* null," or, briefly, L_0—it is the Zero Limit, the limit of the non-appearance of pathogenetic effect. The second mixture requiring special attention is that in the rising series with which there occurs death with acute symptoms in five days. At this point there is enough of the toxic principle free from combination with the antitoxin to produce the effect of 1 M.L.D. of crude toxin. In mixtures below the strength (but above the L_0 point) there is enough free toxic material to cause symptoms, but not sufficient to cause death in the assigned test-time,—a similar state of affairs, in fact, as occurs with sublethal doses of crude toxin alone. This point in the series is denominated by Ehrlich the "*Limes* tödtlich," briefly L_t, the limit of a certainly fatal effect in the test-time. For a particular toxin there are thus these three points to be determined, which are important from the present standpoint—First, the minimal lethal dose; secondly, the amount which will just neutralise one immunity unit of antitoxin—this gives the L_0 value; third, the amount which when mixed with one immunity unit, completely saturates the antitoxin present, and still leaves toxic matter free in sufficient quantity to give the pathogenetic effect of 1 M.L.D. This last amount gives the L_t value. We give

examples of the values found for two of the toxins used by Ehrlich in his original inquiry :—

Toxin No. 7.	Toxin No. 10.
M.L.D. = ·0165 gr. L_{+} = 1·26 gr. *i.e.* 76·3 M.L.D. L_0 = 0·9 gr. *i.e.* 54·4 M.L.D. (approx.)	M.L.D. = ·001 gr. L_{+} = 0·0292 gr. *i.e.* 29·2 M.L.D. L_0 = 0·0275 gr. *i.e.* 27·5 M.L.D.
Difference = 0·36 gr. *i.e.* 21·9 M.L.D.	*Difference* = 0·0017 gr. *i.e.* 1·7 M.L.D.

A minor point here, which is at once apparent, is that the immunity unit neutralises different multiples of the simple M.L.D. in the cases of the two toxins. This bears out what has already been said regarding the artificial nature of the unit; the probable explanation of the variation will appear as we proceed, for the present it may be neglected. The important aspect of these examples lies in the question they raise, namely, given that the antagonism between toxin and antitoxin is, as we have seen reason to think, of a chemical nature, is the union to be looked on as of an ordinary simple character, such as occurs between two bodies capable of entering into combination, for instance, an acid and an alkali? If the union were simple, should we not expect that on the addition of 1 M.L.D. to a neutral mixture, death of the test-animal would occur just as if 1 M.L.D. without the presence of any toxin-antitoxin mixture were injected? In one case (toxin 7) we observe that 22 M.L.D., and in the other (toxin 10) 1·7 M.L.D. had to be added to the neutral mixture before death was produced, and we may say that in all the other toxins examined by Ehrlich, similar results to those quoted were obtained; in fact, the case of toxin 10, where the difference between the L_0 and L_{+} values approached near to unity, is to be regarded as quite exceptional. As to the existence of the Ehrlich phenomenon there is no doubt. The observation has been confirmed by Dr. Bulloch (59) working with diphtheria toxin, and by many of Ehrlich's pupils. With regard to the explanation, we shall first of all give Ehrlich's own view, which is as follows:—When bacterial toxins are kept at room temperature, even if under toluol and in the dark, there is, as every worker knows, a gradual loss of toxicity. Mere observation of loss of toxicity may not, however, fully describe the condition of the toxin; for Ehrlich found that a toxin might lose toxicity without losing its capacity of combining with antitoxin. Thus in one case a crude toxin immediately after its filtration had a M.L.D. of ·003 grammes, but nine months later the M.L.D. was ·009 grammes. Notwithstanding this, the amount of toxin saturating completely one immunity unit of antitoxin was the same as before. To the weakened true toxins Ehrlich gives the name of toxoids. Given the existence of such bodies, and taking into account that the weakening in crude toxins is under ordinary conditions often a

very gradual process, it is evidently possible that crude toxin may contain the true toxin in various forms,—may in fact be a mixture of substances which though related to each other, may be very different in poisonous effects. Thus crude diphtheria-toxin would owe its capacity of producing death in four or five days only to the true toxin it contains; its paralytic effects would be due to its toxoids. Given the existence of toxoids, how can the fact of a crude toxin losing toxicity without losing binding affinity for antitoxin be explained? This would be accounted for, if in the ultimate molecular complex of the true toxin the affinities which are responsible for combining with true antitoxin differed from the affinities responsible for the toxic action. This is what Ehrlich supposes to be the state of affairs, and he calls the binding affinities or side-chains the *haptophorous* affinities, and the toxic affinities or side-chains the *toxophorous* affinities. The toxoid could be derivable from the true toxin if the toxophorous affinities became weakened. In the particular crude toxin alluded to, in which a diminution of toxicity was observed, it could be supposed that no diminution of capacity to saturate antitoxin occurred, — that the toxophorous affinities were affected, while the haptophorous remained as potent as formerly. It is, however, evidently possible that both the haptophorous and toxophorous affinities of the true toxin might be affected, and to account for the "Ehrlich phenomenon" it is necessary to suppose that this happens. It is evident that with a formation of toxoid by a weakening of the toxophorous group, one of three possible eventualities may occur in the haptophorous group of the true toxin; either it might have its potency increased, forming what Ehrlich calls protoxoid, or its potency might remain unchanged (syntoxoid), or its potency might be diminished (epitoxoid). Suppose a crude toxin contained true toxin and epitoxoid, and these in the proportion of 9:1, a neutral mixture of this crude toxin with antitoxin might be represented thus: 90 parts toxin-antitoxin combination + 10 epitoxoid-antitoxin combination = physiologically neutral mixture. If to this we add crude toxin containing 10 parts true toxin, it is evident that the stronger affinity of the true toxin would turn the epitoxoid out of the epitoxoid-antitoxin combination; there would then be 100 parts toxin-antitoxin combination + 10 parts uncombined epitoxoid + free epitoxoid derived from the crude toxin containing the 10 parts true toxin. The result of injecting such a mixture would correspond to the case where an animal suffers from symptoms which, if fatal, will not kill it in the test-time. Suppose, however, crude toxin containing 11 parts of true toxin were added to a neutral mixture, the condition of affairs would now be: 100 parts toxin-antitoxin combination + 1 part toxin uncombined + 10 epitoxoid uncombined + the free toxoid derived from the crude toxin containing the 11 parts true toxin. If the "1 part toxin uncombined" corresponded to the amount of true toxin in a M.L.D., evidently the animal would die in the test-time. This is practically what occurs when the difference between the L_0 and the L_{+} values, as has been found to hold good in all cases examined, is

greater than 1 M.L.D. If a crude toxin contains much epitoxoid, then the true toxin in the moieties added to a neutral mixture turns out the epitoxoid of the original crude toxin used for making the neutral mixture. These when free are relatively non-pathogenetic, and it is not till they are all turned out, and in addition an amount of true toxin, equal to that present in 1 M.L.D. of the crude toxin, is left unsaturated with antitoxin, that acute fatal effects are produced. This capacity of a molecule with strong haptophorous affinities to turn a molecule with weak haptophorous affinities out of a toxin-antitoxin mixture is the essential factor, according to Ehrlich, of the "Ehrlich phenomenon." There are, however, other points, two of which may be mentioned here. First, it follows from Ehrlich's view that a toxin molecule combined by means of its haptophorous affinities with an antitoxin molecule is inert. Its toxophorous affinities are probably intact, as is shewn by the occurrence of slight symptoms when the less pathogenetic toxoid is turned out of the toxoid-antitoxin combination by the addition of fresh toxin. It may be asked, why this inertness? This is explained by the second consequence of Ehrlich's hypothesis which we shall presently notice, namely, that a toxin molecule when it gains entrance to the animal body is anchored in the cell in which it acts by means of the same haptophorous group by which it is capable of combining with antitoxin, and unless it be so anchored to the cellular protoplasm, the toxophorous affinities can have no effect in upsetting the metabolism of that protoplasm, *i.e.* cannot produce disease effects. Thus the toxin-antitoxin combination can pass to and fro freely in the bodily fluids, and though it may contain powerful toxophorous affinities, these cannot act, because the molecule of which they form a part is firmly anchored to another molecule. We shall later inquire on what evidence such conceptions have been based. It will be convenient meantime to deal with Ehrlich's further views on the nature of toxins.

In examining the L_0 and L_t values in the case of a number of diphtheria toxins, Ehrlich (103) observed that the toxin units (a toxin unit being the amount of a simple M.L.D.) in the L_0 value followed an apparent law in that in the series of toxins examined the figures 25, 33, 50, and 100 frequently recurred; the lower of these figures, it is evident, bear very simple relationships to the higher. This appeared to him to indicate that the degeneration of the crude toxin did not occur at random, but that the amounts of the degenerated bodies produced were in proportional relationships to one another. It may be, as Ehrlich suggests, that the original toxin molecule splits into two toxoid molecules by dichotomy, or into three (trichotomy). Thus, if we imagine a crude toxin to contain only two elements, toxin and epitoxoid, and to give an L_0 value of 50 (*i.e.* when one immunity unit of antitoxin supposed to be capable of neutralising 100 M.L.D. neutralises 50 M.L.D. of the toxin under consideration), it is manifest that the proportion of toxin to toxoid must be 1 : 1. We have already pointed out that the serum used by Ehrlich as the test-serum against which all toxins are measured, must

originally have been chosen somewhat at random. That its original supposed neutralising value (100 M.L.D.) could not be taken as absolute, was shewn by Ehrlich's later results, when such different values for L_0 were obtained. Taking for granted that the recurrence of figures in the L_0 values bearing such simple proportions to each other as 25, 33, 50, 100, really indicated that of the original true toxin as produced by the bacilli, three-quarters or two-thirds or a half had undergone in a definite time a particular degeneration, it is evident that the number of true toxin units originally represented in the crude toxin could not have been less than 100, as that is the least common multiple of the true toxin units remaining in the examples of degenerated toxin examined. In fact it was probably more, as L_0 values of slightly over 100 were observed. If it were over 100, the probability,—from the simplicity of the proportions,—was that it was a multiple of 100. Turning from the consideration of the L_0 values observed, the L_t values demand even more consideration from the point of view of an attempt to arrive at an idea of the number of binding affinities in the immunity unit. If, as has already been pointed out, we had to deal with an absolutely pure poison, *i.e.* one containing no degenerated toxin but only true toxin, the difference between the L_0 and L_t values would be 1 M.L.D. Such a crude toxin has never been observed,—the difference, as we have seen, has always been greater than unity. With regard to the number of simple M.L.D. in the L_t values Ehrlich has observed a value of 133, and Madsen one of 160. Thus, there never has been observed a toxin where the L_t value did not contain considerably less than 200 M.L.D. As we have seen, the expression of the number of the binding equivalents of true toxin units must be over 100, and probably is a multiple of 100, so that in the meantime 200 may be taken as the possible expression of the binding equivalents present in one immunity unit. This means that in the amount of crude toxin capable of neutralising one immunity unit of the test-serum there are at least 200 binding affinities, *i.e.* if pure toxin could be obtained one of Ehrlich's immunity units would neutralise 200 M.L.D. The equivalent of a simple binding group is that portion of true toxin which contains a simple M.L.D. for a guinea-pig of 250 grammes; but in relation to antitoxin such an equivalent may be represented by the less poisonous constituents of the crude poison. In the dose present in a mixture of L_0 value, the number 200 represents the sum of the binding affinities of toxin and toxoid. Having arrived at the figure 200 as expressing the number of binding affinities probably present in the toxin of the L_0 mixture, Ehrlich proceeded to study the effects of taking an amount of toxin and only partially saturating it with antitoxin; in other words, having determined the L_0 and L_t values of a toxin a number of either the one or the other values were taken, and a fraction of an immunity unit of serum being added to each, the properties of the unsaturated mixtures were studied by investigating what fraction of such a mixture was a M.L.D. In one particular toxin Ehrlich found the M.L.D. to be ·024 c.c. and the L_t dose 2·05 c.c., *i.e.* 85

M.L.D. If now a mixture containing the L_t dose and $\frac{180}{200}$ of an immunity unit of antitoxin were made up, it was found that this was sufficient to kill $3\frac{1}{2}$ guinea-pigs, one containing $\frac{160}{200}$ could kill 10 animals, and one containing $\frac{50}{200}$ could kill 60; that is to say, the 150 binding units unsaturated in the last case could kill 60 animals, and thus the 50 saturated may be taken as capable of killing 25 (the difference between 60 and the full value of the L_t dose, namely, 85). In this last part of the toxin which shews greatest affinity for antitoxin it is evident that each binding equivalent represents only half a toxic equivalent. Ehrlich would explain this by supposing that it consisted of equal parts of a toxin and of a toxoid, each of which had equal affinity for antitoxin. In this toxin as a whole the greater part must have been built on the same plan, for the next 110 binding affinities corresponded to 50 toxic equivalents, *i.e.* nearly one-half toxin and one-half toxoid; the next 20 binding units, however, corresponded only to $6\frac{1}{2}$ toxic units, *i.e.* roughly there must have been one part of a toxin and two parts of a toxoid—both having, of course, less binding affinity for antitoxin than the previous. Ehrlich, generally speaking, classifies the different elements of a crude toxin according to their affinity for antitoxin; first those with greatest affinity, the prototoxins, with their corresponding substances with equally great affinity but less toxicity, the prototoxoids; next those with less affinity but with still powerful toxicity, the deuterotoxins (sometimes called mesotoxins), which also have corresponding deutero-toxoids; next the tritotoxins and tritotoxoids. According to Ehrlich's general nomenclature, they would all be syntoxins and syntoxoids. But there are also the poisons with haptophorous affinities, weaker than any true toxin haptophores, and also weakened toxophores. These weakened bodies correspond to the epitoxoids, and Ehrlich now prefers to call them toxons. He has found evidence of these in very young diphtheria cultures, and inclines to the belief that they are actually formed by the bacilli without going through a previous more highly toxic stage. These toxoids might be called primary toxons. But, as has already been stated, he attributes the weakening observed in crude toxins when they are kept under ordinary conditions to the development from toxins of toxoids which might be called secondary toxons.

From analyses of crude toxins by the partial saturation method at different periods after filtration, Ehrlich considers that in many cases the proto-, deutero-, and trito-toxin moieties degenerate into corresponding toxoids or into lower toxoids (*i.e.* bodies with not only weaker toxophorous but weaker haptophorous affinities) in definite proportions in a given time. Thus in the case of the proto- and deutero-toxin, present in a fresh bouillon filtrate, degeneration may occur very rapidly in half of the amount present, while the other half may persist unchanged for a long period; there is some evidence of similar changes occurring in trito-toxin (these Ehrlich often refers to as the hemitoxin of the corresponding toxin,—be it proto-, deutero-, or trito-). Such occurrences would serve to explain

the observation that after filtration the toxic power of a crude toxin may rapidly decrease; but after a time this degenerative process may come to an end and the toxicity remain nearly constant for a long period. To represent graphically the composition of crude toxins Ehrlich introduced the method of plotting, the result of which he called toxin spectra: in these the binding affinities are represented on the horizontal line (abscissa) and the proportion of the toxicity present to the absolute toxicity on the vertical ordinate; an example is found in Chart 3.

Such in brief outline is the conception which Ehrlich has formed of the ultimate nature of the toxic action of crude diphtheria toxin. That substance, under the conditions which ordinarily obtain, does not owe its toxicity to one substance, but to a number of toxic agents, though these probably are all derived from one product of the bacterial protoplasm, or are all built up in that protoplasm on the same plan. As these agents pass into the fluids in which the diphtheria bacilli are growing, whether that fluid be within or without the animal body, they are present in two chief forms, a powerful form—true toxin—causing acute symptoms, expressed locally in œdema generally, in fever and cardiac weakness, and a weaker form—toxon—causing after an interval of time the paralyses common in the disease as it occurs in nature. Subsequently, at least in ordinary bacterial filtrates, the toxins degenerate into substances at present indistinguishable from toxons. Further, according to the hypothesis, the affinities in the different toxins through which the combination with antitoxin is effected differ from the affinities which produce the essentially toxic action. It is evident that, as has been already remarked, the method by which certain purely chemical properties in substances are deduced from their toxicological action is a novel one, though in the circumstances it is the only one, seeing that present chemical methods are inadequate for obtaining pure samples of the substances under investigation.

Criticism of Ehrlich's Views by Arrhenius and Madsen.—It is thus not surprising that the hypothesis should have been criticised, or rather that other interpretations of the facts observed should have been advanced. Of the investigators who have done this the most notable are Madsen (197) and Arrhenius (10). These observers have worked in conjunction, the former approaching the questions from the pathological standpoint and the latter from that of physical chemistry. Madsen (196) published, in 1899, the result of work in Ehrlich's laboratory on the poison tetanolysin. This substance has been alluded to as occurring in some samples of crude tetanus toxin. It has the capacity of hæmolysing red blood-corpuscles, especially those of the horse and rabbit. When it has been present in a crude tetanus toxin used for immunising a horse, an antitetanolysin is developed. This appears in the animal's serum, and has the capacity of protecting susceptible red blood-corpuscles against the hæmolysing effects of the tetanolysin. The interactions of the two opposing bodies can be studied by means of test-tube experiments. All that is required is to mix appropriate amounts of the

two substances, to leave them together, and then test the amount of interaction during a given time by adding a suspension of red blood-corpuscles and noting whether or no hæmolysis occurs. The facility with which this can be done as compared with the laborious and extended observations required when, as with diphtheria toxin, an animal's body is the field of experiment, makes it easy to accumulate very extensive data in an extremely short time. In one of his earlier papers Ehrlich (103) admitted that it was impracticable in making up a spectrum to test the effect of adding to the L_t dose every two-hundredth fraction of an immunity unit. With the amount of tetanolysin necessary for complete neutralisation of a given amount,—arbitrary, of course,—of antitetanolysin, such fractional investigation was quite easy. If, in the case of tetanolysin, fractions of the neutralising body differing by large amounts were used, *i.e.* if a procedure were adopted similar to that usual with diphtheria investigations, results comparable with those found with diphtheria toxin were obtained; thus if $\frac{1}{13}$ of the total neutralising amount was added, $\frac{1}{5}$ of the total hæmolytic power was removed, the next $\frac{1}{5}$ removed $\frac{2}{5}$ of the total hæmolytic power, and the following $\frac{1}{4}$ removed $\frac{1}{10}$ of the total toxicity. By such observations it was possible to construct a spectrum showing proto-, deutero-, and trito-toxin zones just as exist in Erhlich's conception of the constitution of the crude diphtheria poison. But if to the moieties of the tetanolysin there were added moieties of the antitetanolysin differing from each other by very small increments, the neutralisation could be represented by a very regular curve without the sudden drops which occur in Ehrlich's spectra, and which are interpreted by him as indicating the termination of the saturation of one component and the commencement of the saturation of another. Basing their argument on the gradual nature of the neutralisation of the tetanolysin Arrhenius and Madsen compare what takes place with what occurs in the neutralisation of an alkali by an acid. This comparison was facilitated by the knowledge that alkalis are hæmolytic agents. This had been observed by Danysz, and had been employed by him as the basis for a criticism of Ehrlich's views similar to that of Arrhenius and Madsen. These observers, however, extended its application. They draw attention to the effect on the hæmolytic action of 1 c.c. of ammonia in normal solution of adding normal hydrochloric acid in varying fractions. They point out that the addition of ·25 c.c. of this acid removes one-quarter of the hæmolytic action of the base, ·5 c.c. one-half, and ·75 c.c. three-quarters. The antihæmolytic action of the acid is thus directly proportional to its amount. On the other hand, a different result is obtained if, instead of using a powerful acid, a weak acid, boracic acid, is employed as the "antitoxin." Here 1 c.c. normal acid neutralises only 50 per cent of the ammonia, 2 c.c. 60 per cent, 4 c.c. 80 per cent, and in fact neutralisation is never really complete. Applying Ehrlich's deductions, Arrhenius and Madsen say: "In other terms ammonia is not a simple body, but consists of several components of different toxicity (and these toxicities are in simple

reciprocal proportions). Of these compounds the toxin with the greatest chemical affinity is first neutralised." They put a different interpretation on their observations. According to the conceptions of modern physical chemistry, the strength of an acid or a base depends on the ready electrolytic dissociation of the hydrogen or hydroxyl (OH) ions which their molecules contain. In the case of the union of hydrochloric acid and caustic soda electrolytic dissociation is ready, and almost wherever the bodies are brought together the neutral salt NaCl is formed and no free H or OH ions remain. In the case of weak acids or bases, such as boracic acid and ammonia, dissociation is weak, and thus certain molecules of the two bodies may remain in contact for a time without

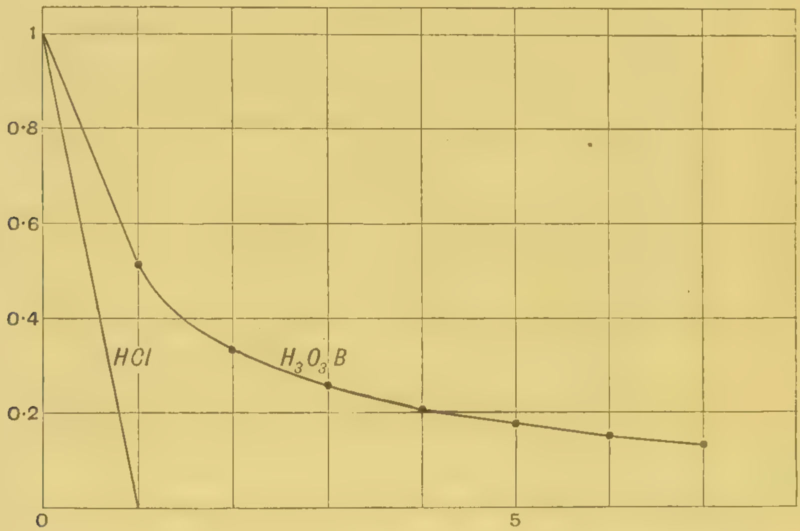

CHART. 1—Graphic representation, given by Arrhenius and Madsen, of the neutralisation of ammonia by hydrochloric acid on the one hand, and by boracic acid on the other. The vertical ordinate represents one equivalent of ammonia; on the horizontal abscissa the divisions represent equivalents of acid. In the case of the hydrochloric acid it will be seen that one equivalent of the acid completely neutralises the equivalent of ammonia, and the reaction is thus represented by a straight line. With boracic acid one equivalent neutralises only half of the ammonia, and even when seven equivalents are present there is still some ammonia free. The reaction is thus represented by a curve, and resembles the curve in Chart 2.

any change occurring. Further, and this is even more important, the ammonium borate formed may be dissociated into its constituents; in other words, the reaction between their constituents is reversible. Now, in comparing the curve obtained in studying the hæmolytic action of tetanolysin with that obtained with the hæmolytic action of ammonia a great similarity was observed, and therefore Arrhenius and Madsen have advanced the view that tetanolysin and antitetanolysin possess for each other a relatively weak affinity, that the union is thus slow, and that the reaction is reversible, the lysin-antilysin compound being capable of splitting up into the molecules from which it was derived. Both reactions can, it is held, be calculated according to what is known as the Guldberg-Waage law of mass action, that "the rate of chemical action is proportional

to the active mass of each of the reacting substances." From the fact that observations made along similar lines on a diphtheria toxin by Dreyer and Madsen (90) revealed no evidence of sudden transitions in the effects of fractional saturation by antitoxin, but a slow progress which could be expressed by a curve, Madsen is inclined to extend his interpretation of the lysin phenomenon to explain the composition of crude

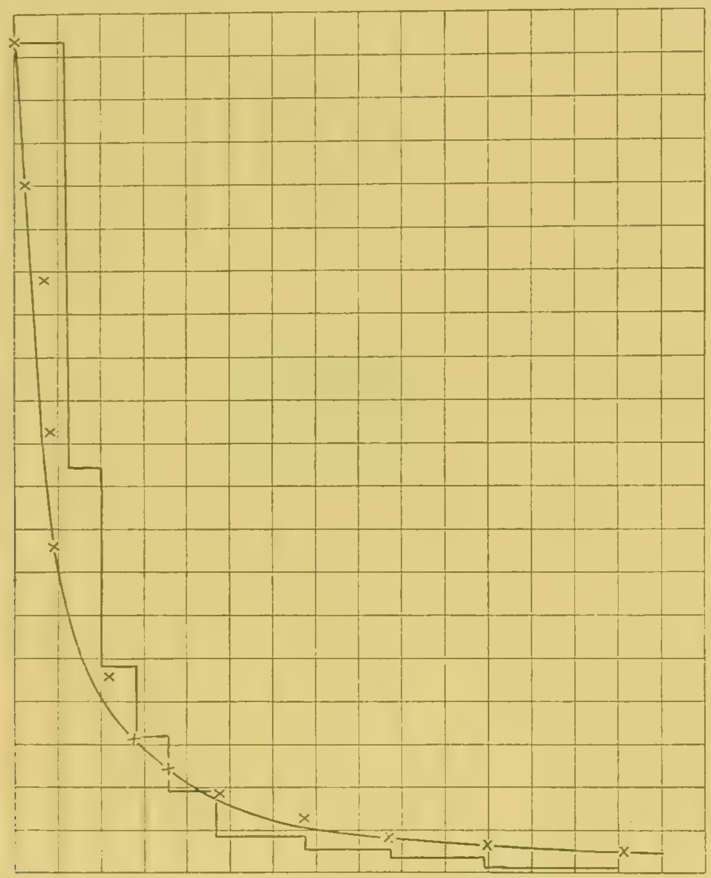

CHART 2.—Graphic representation of neutralisation of toxin by antitoxin. The doses of antitoxin are represented along the horizontal line (axis of abscissa), while the toxicity corresponding to each dose is represented by the vertical ordinates. The crosses in relation to the curve chronicle the actual observations; the curve itself is derived from the mathematical interpretation of the inter-relations of the observed facts; the close correspondence of the observed with the calculated values is apparent. The stair-step line shews how, on the Ehrlich hypothesis, the facts would be interpreted,—it is in fact a spectrum. (Compare with right-hand part of Chart 3.)

diphtheria poison. According to such a view Ehrlich's observations on the partial saturation of diphtheria toxin are not to be explained by supposing that a number of bodies with different affinities and different toxic actions are present in the crude toxin; but by supposing that the toxin and antitoxin have a weak affinity for each other and that the reaction is reversible. In this connexion the difficulty is encountered that apparently toxin and toxoid have different effects, the former producing

the acute symptoms and the latter the paralytic. In the particular toxin which Dreyer and Madsen jointly investigated, they found what they took to be evidence that the same body can be responsible for the two classes of effects, and that these are to be explained by a consideration of differences of dosage.

Ehrlich's Reply to Arrhenius and Madsen.—The original views of Ehrlich and the later criticism of Madsen and Arrhenius are those which at present hold the attention of pathologists, and from the nature of the case are likely for a considerable time to afford material for discussion. As no definite opinion can possibly be expressed as to the merits of the two views, we must be content with outlining the points of the discussion, which is at present only in its earlier stages. Ehrlich (105) holds to his original view unshaken, and criticises the results of Arrhenius and Madsen in that, unlike ordinary physico-chemical researches, in the tetanolysin work purity of reagents was unattainable. He insists on the necessity for each toxin being considered by itself, and objects to generalisations being made even regarding one particular toxin until many examples of this toxin derived from different strains of bacilli have been examined; and he cites many examples of differences in not only the components, but also arrangement of components, in different samples of diphtheria toxin examined by him. For instance, great difficulties have arisen as to the interpretation of a phenomenon observed by Dreyer and Madsen (91) in the case of a particular diphtheria toxin, in that the L_0 dose for the guinea-pig was not the L_0 dose for the rabbit. Ehrlich, while explaining the occurrence by supposing the presence in this particular toxin of certain degenerated toxoids to which the rabbit may be particularly susceptible, brings forward the new observation that the greater susceptibility of the rabbit is not observable with all strains of diphtheria toxin, as he has observed toxins where the L_0 dose was the same for both the rabbit and the guinea-pig. Ehrlich, however, bases his chief objections to Madsen's criticisms on what he holds to be a fact, that diphtheria toxin-antitoxin reactions cannot always be expressed in curves. In one case there were 50 M.L.D. in the L_0 value of the toxin. With partial saturation of this crude toxin, no free toxin appeared with the fractions greater than half saturation. Below this point, for every $\frac{2}{200}$ths less antitoxin added, 1 M.L.D. appeared free. In another case (see Chart 3) of similar partial saturation, in the fractions between $\frac{176}{200}$ and $\frac{115}{200}$ the value of each toxin equivalent was only $\frac{1}{20}$; between $\frac{115}{200}$ and $\frac{72}{200}$ each unit contained 1 M.L.D.; from $\frac{72}{200}$ to zero each unit contained only $\frac{1}{2}$ M.L.D. Here again there is no evidence of a gradual neutralisation of one substance. In the former example given there was a definite uniform toxicity equal to $\frac{1}{2}$ M.L.D. for each binding unit up to half saturation, and then the disappearance of any evidence of further true toxin being present in the crude product. In this second instance up to the 72nd binding unit there is hemitoxin, with which each binding unit represents true toxin present in $\frac{1}{2}$ M.L.D.; then there is the sudden appearance of a toxin of which each binding unit repre-

sents the true toxin present in 1 M.L.D.; this lasts till the 115th unit is reached. These saltations in the spectral analyses are, according to Ehrlich, not capable of expression by a curve, nor are they compatible with the idea that the occurrences in the Ehrlich phenomenon are to be looked on as due to a reversible reaction between two substances. Ehrlich holds that Arrhenius and Madsen are in error in transferring their deductions made on tetanolysin to the observed facts regarding diphtheria toxin, in that the avidity of the former for its antitoxin is small, and thus the reaction being slow can be expressed in a curve; on the other hand, the avidity of diphtheria toxin, in its purest forms, for antitoxin is great, and, as in the first example cited above (that containing 50 parts hemitoxin), can be expressed by a straight line. Further, they are mistaken in that while they admit the existence of toxoids, they only admit that they have obtained evidence of the existence of prototoxoids, *i.e.* of bodies having a more powerful haptophorous group than the true toxins while possessing a weaker toxophorous group.

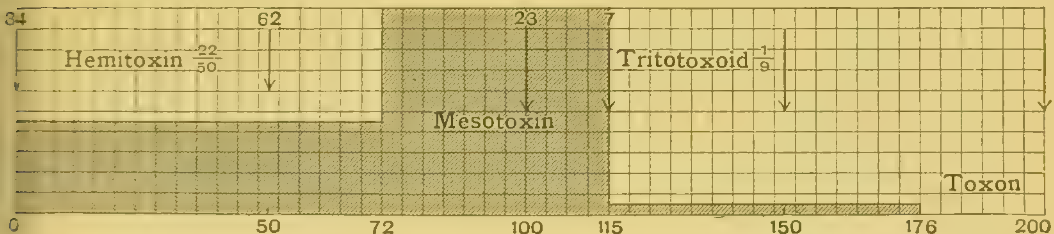

Chart 3.—Spectrum given by Ehrlich of the toxin referred to in the text, in which the moiety with strongest haptophorous affinities (marked hemitoxin,—really a hemitoxin of a prototoxin) shewed less toxicity than that possessing the next strongest affinities (marked mesotoxin,—really to be looked on as a deuterotoxin). In the tritotoxin zone most of the toxin has degenerated into toxoid.

The occurrence of these would not satisfy the facts Ehrlich has observed, *e.g.* the occurrence of prototoxin in what would be expected to be a deuterotoxin zone, *e.g.* mesotoxin zone in Chart 3. Ehrlich gives as an example here what would happen in the neutralisation by alkali of a mixture of hydrochloric acid with prussic acid. Here the hydrochloric acid would correspond to the prototoxoid in that while it was the more powerful acid *qua* acid, it is the weaker toxic agent to protoplasm. This acid would be wholly neutralised before the neutralisation of the prussic acid commenced, and the neutralisation of the latter would proceed as if no hydrochloric acid had been present. Arrhenius (7) in his reply upholds his earlier position, that the tetanolysin-antitetanolysin reaction is best interpreted by comparison with the neutralisation of boracic acid by ammonia, and denies that, as Ehrlich holds, the neutralisation of, say, an acid by a mixture of a strong and of a weak base could ever resemble neutralisation of an acid by a single weak base. With regard to the cases in which Ehrlich has observed in spectra (*v.* Chart 3) zones of great toxicity interposed between zones of less toxicity, it is probable that Arrhenius and Madsen would hold that

there were in such cases a series of bodies acting, and that the phenomena when graphically represented are to be interpreted as due to the superposition of different curves. They have, however, apparently not admitted that in any circumstances the diphtheria toxin-antitoxin reaction can be represented by a straight line.

That weakened toxins do exist there can be no doubt. In diphtheria evidence that the substances which kill slowly by paralysis are the same as those which kill quickly with general symptoms, has been found in the experiments of Dreyer and Madsen (91), who shewed that if the powerful toxins in a mixture were neutralised by antitoxin (the paralysis-producing bodies being left intact), and if such a mixture were used for producing immunity, the immunity was effective against both the strong and weak toxins.

Present Position of the Controversy.—While the controversy as to the ultimate interpretation of the facts observed must be stated to be still going on, there is a growing accumulation of data to shew that a great many toxin-antitoxin reactions take place along the same lines as those relating to diphtheria and tetanolysin. These are summarised by Madsen (197), who has shewn such similarities in the antagonism of ricin and antiricin,—with Walbum (200),—of rennet and antirennet, of the venoms of cobra, rattlesnake, and water moccasin venoms with their antibodies, of botulismus toxin and antitoxin (198), and also in the antagonism of saponin and cholesterin,—with Noguchi (199). (This last case is specially interesting, as it is an example of a toxin and antitoxin reaction occurring in bodies whose constitution is more or less known.) In further investigations he has adduced experimental evidence for the reversibility of the toxin-antitoxin reaction. This evidence consisted in the separation by dissociation of toxin from its combination with antitoxin. In any mixture where neutralisation is taking place, there is at any moment an equilibrium between the amount of free toxin, the amount of free antitoxin, and the toxin-antitoxin combination which has already been formed. This equilibrium is disturbed at any moment by a change in the amount of any of the bodies concerned. What may be called the normal disturbance of the equilibrium results from the constant formation of the toxin-antitoxin body, but it will be disturbed if, otherwise than by entering into this combination, the amount of either the toxin or antitoxin in the mixture is diminished. If this happens, then the reversibility of the reaction will be indicated by a new equilibrium being established by the splitting up into its original constituents of the toxin-antitoxin body. Madsen and Walbum (200) adduce evidence of such an occurrence. A mixture of ricin and antiricin was taken at a period in the reaction when there was so little free ricin that no toxic effect in guinea-pigs was traceable. Two c.c. of such a mixture were poured on the surface of a tube of 10 per cent gelatin, and allowed to stand at 2-3° C. for 66 days, when the fluid was poured off and the surface of the medium washed with sterile salt solution. The upper ½ cm. of the gelatin was mixed with 1 M.L.D. of the toxin and injected into a guinea-pig with no result. The deduction

is that free antitoxin had diffused into the gelatin from the neutral mixture in sufficient amount at least to neutralise this amount of toxin. Part of the 10 cm. of the gelatin below the upper zone killed a guinea-pig in 4½ days. The rest was mixed with 400 immunity units of antitoxin, and on injection produced a temporary œdema. Thus, there was evidence that both free antitoxin and, what is more significant, free toxin could be recovered from a previously neutral mixture of the two bodies. The interpretation put on the experiment was that the toxin-antitoxin combination could be split up, and that thus the reaction was reversible. On the other hand Calcar, working in a similar way with diphtheria toxin and antitoxin, states that the longer the mixtures are kept standing before being placed on gelatin, the less evidence is there of diffusion from the mixture into the gelatin. There is no doubt that this question of the determination of neutralisation and the definition of the term is of imminent practical importance. In the application of the toxicological method of determining neutralisation a mixture will appear neutral as long as there is a certain excess of the non-toxic substance, even though complete saturation of the toxin has not occurred previous to injection into the test-animal. If, as we shall see reason for supposing, the toxin is absorbed more quickly than the antitoxin, the portion of the former substance still free at the moment of injection may be distributed over the body and produce a toxic effect. The superfluous antitoxin injected being more slowly absorbed, may yet be present in sufficient quantity to prevent the free toxin having a fatally pathogenetic effect. It may either combine with toxin free in the body, *i.e.* the combination *in vitro* may be continued *in vivo*, or the probably more complicated therapeutic effects of the antitoxin may come into play. There is no doubt that this question of the exact neutralisation-point of a toxin-antitoxin mixture is full of difficulties, and it may be that some of the results hitherto chronicled will require revision. As an instance of the complexity of the subject, it may be said that Morgenroth (246) has shewn that the discrepancies observed by Dreyer and Madsen between the L_0 dose of diphtheria toxin disappear if the injection be made intravascularly in each case (in the guinea-pig injection directly into the ventricle of the heart being employed), and if the mixtures before injection are kept for 60–80 minutes at 40° C. followed by 24 hours at 21 C°. The necessity for care in the estimation of neutralisation was further shewn by Wassermann and Bruck (347). These observers shewed that if a mixture of tetanus toxin and antitoxin apparently neutral under ordinary conditions were, within 1 hour of mixing, injected into the foot of an animal along with a dose of suprarenal extract sufficient to cause contraction of the blood-vessels, death now occurred. This is due to the fact that, as shewn by Meyer and Ransom tetanus toxin is absorbed by the axis-cylinders of the peripheral nerves while antitoxin passes into the body by means of the blood-stream. In the experiments of Wassermann and Bruck, the body thus sorted out the two free moieties of the constituents of the toxin-antitoxin mixture,

the union *in vivo* was prevented, and the toxin had the opportunity of working its usual toxic effect. It was, however, further found by these observers that if more than one hour elapsed between the mixture being made up and its injection along with the adrenalin injection, then death did not occur. In other words, the bodies were now completely combined.

In recent times there has been a considerable tendency in various directions for an attitude to be taken up independent of that of either of the protagonists in this controversy. There have been for a long time certain facts which seemed difficult of explanation on the view that the toxin-antitoxin reaction took place on ordinary chemical lines. Chief among these were the observations by Dreyer and Madsen (91) already referred to, that a mixture of diphtheria toxin and antitoxin neutral for the one animal species might not be neutral for another species. There was also the observation by Roux and Vaillard, that a tetanus toxin-antitoxin mixture neutral for a normal guinea-pig might not be normal for a guinea-pig previously infected with a pathogenetic vibrio. It appeared that the question of toxin-antitoxin reaction must be looked at not merely as a reaction in which two foreign substances took part, but one in which a third element, namely, the animal in which the reaction was taking place, had to be considered. It is thus not surprising that in many minds doubts should exist as to the possibility of an ordinary simple chemical explanation of this phenomena being sufficient. In this connexion we may first refer to the criticisms of Bordet (40). We shall see later that, with regard to another aspect of Ehrlich's hypothesis, this observer is inclined to think that reactions similar to the toxin-antitoxin reaction may be looked on not as the result of actual chemical union, but as analogous to the taking up by a texture of a dye; here we have to do with Bordet's views on the toxin-antitoxin reaction itself. These are based on certain phenomena observed in the neutralisation of a hæmolytic poison and its antitoxin,[1] and Bordet's main position is that when the toxin comes in contact with excess of antitoxin it does not merely combine with a moiety corresponding to its amount, but it affects the whole of the antibody present. The evidence on which this opinion rests is of the following nature:—The amount of the toxin necessary to produce hæmolysis in a certain amount of blood was ·05 c.c., the time occupied being half an hour, and the amount of antitoxin necessary to neutralise this amount was ·3 c.c. Now, a mixture of 1·2 c.c. of toxin and ·3 c.c. antitoxin did not effect an hæmolysis in less than 70 minutes. Bordet states that, according to Ehrlich's view, there should have been ·9 of free toxin in this mixture, *i.e.* eighteen times the amount necessary to cause hæmolysis in half an hour. Bordet also made what, we shall see presently, is a most important observation, namely, that if to a dose of antitoxin sufficient to neutralise a given amount of toxin the latter be added in two fractions with an

[1] The hæmolytic agent is the alexin of normal serum which we shall have to discuss at length later. As we shall see, it does not act directly on the corpuscles but by the intermediary of another body. As, however, this is quite immaterial to the present discussion we omit all reference to the complication.

interval of time between them, the antitoxin is no longer sufficient for neutralisation. He further found that though a small amount of free toxin could hæmolyse the test-dose of corpuscles more quickly than a large amount of a toxin which was being acted on by antitoxin, yet if an excess of corpuscles were employed in each case, then in a given time a much greater amount of hæmolysis resulted with the partially combined than with the completely free toxin.

This work undoubtedly comes into line with the views of other observers, who find a solution of the difficulties by considering the phenomena explicable on the supposition that in the toxin-antitoxin reaction there is not a chemical combination in the ordinary sense of the word, but that we have here an example of the interaction of bodies in the colloidal state. According to this view the relation of the antitoxin to the toxin is one of what is denominated *adsorption*. The smaller molecule of the toxin is entangled in the large molecule of the antitoxin, very much in the way in which a dye is entangled in the structure of a thread without entering into combination with it. This position was fully discussed in a congress of physical chemists held in 1904, at which both Ehrlich and Arrhenius were present (9). Here certain observations of v. Dungern (93) were adduced as fatal to the idea that the toxin-antitoxin reaction is reversible. The experiment was as follows:—The M.L.D., L_0 and L_t, values of a toxin were determined in the usual way. To a series of tubes containing single immunity units amounts of toxin corresponding to about the L_0 and L_t values were added, not all at once, but each in two moieties. The mixtures containing the first moiety were allowed to stand for a considerable period—often for 24 hours—and then in each case the second moiety was added, and the whole left for some hours longer. The effect was that what corresponded to the L_t value—*i.e.* the value which contained one M.L.D. free—was found to be lower than if all the toxin had been added at one time to the immunity unit. Thus, when tested in the ordinary way, the L_0 dose was ·6 c.c. and the L_t dose ·78 c.c., but when to one immunity unit ·6 c.c. toxin was added in two moieties, it was found that the final mixture was no longer neutral, but killed a guinea-pig in the test-time—in fact the fatal dose was ·59 c.c. Thus the L_t dose was now actually less than the original L_0 dose. Now, it is held that such a phenomenon could not happen if the toxin-antitoxin reaction were reversible. If, as Ehrlich puts it, we take as an example of a reversible combination the case of acetic acid (representing toxin) acting on alcohol (representing antitoxin), what occurs is quite different. If we make a mixture A by adding to an equivalent of alcohol one-third of an equivalent of acetic acid a condition of equilibrium is obtained. We put this aside for a time and then add the remaining two-thirds of the equivalent of acetic acid. If, at the time of the second addition, we take a mixture B, containing an equivalent of alcohol, and add to it at once a full equivalent of acetic acid, in a very short time the quantities of combinations present in the two mixtures are identical. It was further shown by Biltz during the discussion just referred to that a phenomenon

identical with the Ehrlich phenomenon is observable in inorganic substances in the reaction of arsenic acid with the colloid hydrous ferrous oxide (FeO.OH).

The phenomena of the neutralisation by its antilysin of the lysin produced by the *B. megatherium* has been studied by Craw (74). This observer found that free lysin is present in neutral mixtures and in mixtures containing excess of antilysin, that free antilysin exists in neutral mixtures and in mixtures containing excess of lysin, and that the reaction is at least partially reversible when excess of antilysin is present, but that nevertheless the neutralisation-equation of Arrhenius and Madsen does not hold for all mixtures as it should do if the action were reversible in the sense in which they use the word. Craw concludes that the removal of lysin from a solution by antilysin cannot be interpreted as a purely chemical change, but is more analogous to certain adsorption phenomena.

It is evident that these considerations are of the highest importance, and they open up possibilities which may necessitate reconsideration of the whole subject. The interactions of substances in the colloid state have hitherto received comparatively little attention, and much knowledge is desirable regarding the relationships of molecules which are bound to one another without being actually united. With regard to the subject in hand it is clear that, though Ehrlich has adduced evidence favourable to the Ehrlich phenomenon being explicable by substances in the colloidal state, the parts played by toxins on the one hand and toxoids on the other in the reaction has still to be explained; and further, the existence of a colloid element in the reaction might necessitate a revision of the very definite views advanced regarding the existence of specific haptophorous and toxophorous groups in the toxin molecule.

The Behaviour of Toxin in a susceptible Animal.—We must now pass to consider Ehrlich's views so far as they deal with the nature and origin of antitoxins. First we must ask how, on Ehrlich's view, toxins act on the body. We have seen that he considers the ultimate toxin molecule to possess haptophorous and toxophorous affinities, and that in an *in vitro* combination with antitoxin the haptophorous group saturates a corresponding affinity in the antitoxin molecule. Now, he further holds that when toxin is introduced into the body of a susceptible animal it is fixed in the susceptible cells by its haptophorous group, and that subsequently the essential toxic effect is the work of the toxophorous group. When such a toxin as that of the tetanus bacillus acts in the body, a period elapses between its introduction and the appearance of symptoms. The question arises, Where is the poison located during the period of incubation? According to Ehrlich (97) it has been shewn by Heymans that it rapidly disappears from the circulating blood. This observer injected a lethal dose of toxin into an animal, and immediately afterwards replaced the blood of the animal by transfusing into it the blood of another animal. Notwithstanding this it succumbed to typical tetanus. In the interval between the toxin injection and the

transfusion the poison had thus been taken up by the tissues. Dönitz (87) produced evidence leading to a similar conclusion by studying the dose of antitoxin necessary to neutralise the effect of a given amount of tetanus toxin. The latter was introduced into a vein of one ear of a rabbit, and into a vein of the other ear, after various periods of time, the antitoxin was injected. If the antitoxin were injected before the toxin, 1 c.c. of a 1 in 2000 dilution was sufficient to prevent death; if the antitoxin were injected 4 minutes after the given amount of toxin 1 c.c. of a 1 in 600 dilution was necessary; if 15 minutes elapsed 1 c.c. of a 1 in 100 solution was required. Similar facts were observed with diphtheria toxin. The deduction made is, that during the few minutes elapsing after injection at least one M.L.D. has passed out of the blood where otherwise it would meet and be combined with the antitoxin introduced. After the toxin had passed out of the blood the method by which the antitoxin could act would be along the lines of its specially therapeutic effect. Given that the toxin passes out of the blood, the question of its situation still remains. According to Ehrlich's view of such a disease as tetanus, seeing that manifestly the central nervous system is chiefly affected by the poison, it would probably be there that the toxin would be fixed. In this connexion we have the much-discussed experiments of Wassermann and Takaki. These observers studied the effects of placing the tissue of the brain of the guinea-pig in contact with tetanus toxin, and they found that if the brain were thoroughly bruised in a mortar and mixed with toxin it was capable of neutralising the action of a considerable amount of the poison. They also state that if the emulsion of the brain were injected into an animal it was capable of protecting that animal against the subsequent injection of an otherwise lethal amount of toxin. It was found that in other animals, *e.g.* man, the horse, similar properties were possessed apparently by the brain alone; but in the case of the rabbit the liver and the spleen shared with the brain the fixing capacity. These observations have in the main been confirmed by Metchnikoff (232), Marie (209), Knorr (160), and others. According to Milchner (242), if the mixture of brain emulsion and toxin be centrifuged there is no free toxin in the fluid, and from this it is concluded that the toxin is attached to the débris of the cells. An important question in this connexion is whether the neutralisation of toxin is an attribute only of the brains of animals susceptible to tetanus. This Metchnikoff denies. The frog, though not susceptible to tetanus when kept at low temperatures, shews susceptibility when its external temperature is raised, yet its brain shews no capacity of neutralising tetanus toxin. It may here be remarked that Blumenthal (30) found that if the brain were boiled before being treated with toxin the neutralisation of the toxin did not occur. Metchnikoff's explanation of the phenomenon is that the toxin is entangled in the brain-substance, and that the latter when injected exercises a chemiotactic influence on the leucocytes of the animal which englobe and destroy not only the brain-substance but the entangled toxin. In this connexion it must be remarked

that the problem of the possibility of fixation of tetanus toxin by brain-cells carries with it a consideration of all the questions raised as to the true nature of the *in vitro* combination of toxin and antitoxin, with the difference that from this standpoint they are incapable of elucidation. For instance, in contradiction of Milchner's results, Danysz (76) found that if a neutral mixture of cerebral substance and tetanus toxin were macerated with salt solution a certain amount of toxin reappears in the fluid. It is evident that, if this be correct, the question of the reversibility of the reaction of toxin with an antagonising substance appears in a fresh form.

Apart from the work of Wassermann and Takaki several points may be brought forward in favour of the possibility that when tetanus toxin disappears from the circulation it is fixed in susceptible cells. Some of these are of an *a priori* nature and are derived from the analogy of what occurs with probably analogous bodies. Thus Sachs (299) has studied the hæmolytic action of the poison of a spider which, as we have seen, there is every reason to believe belongs to the same group as the soluble bacterial toxins, and he has found that while it dissolves the red blood-corpuscles of the rabbit it has no effect on those of the guinea-pig or dog. When the poison was brought in contact with the latter, not only did it not affect them, but if the mixture were centrifugalised the toxin was found free in the supernatant fluid, not having become in any way fixed to the cells. On the other hand, if the stromata of susceptible corpuscles were treated with the poison then fixation to the protoplasm could be observed. More direct evidence of fixation in susceptible cells is found in Ransom's observations on tetanus in susceptible animals. This observer found that, if some excess of the lethal dose of toxin were injected, evidence of free poison could be found in the organs of the body but not in the brain, in which the poison absorbed was presumably fixed in the cells. Additional evidence is also found in the work of Meyer and Ransom, who have shewn evidence for believing that tetanus toxin is absorbed into the system by the axis-cylinders of the motor nerves. In an animal into which antitoxin in great excess has been injected, and in which the blood is in consequence powerfully antitoxic, a fatal tetanus will be contracted if a M.L.D. be injected into a peripheral nerve. There is thus considerable evidence of the fixation of toxin in susceptible cells. Some confusion has been introduced into the discussion by its being in some quarters taken as a corollary to Ehrlich's position that toxin is only fixed in the cells on which the greatest pathogenetic effect is manifested. This is by no means a necessary consequence, as will be at once evident when we look at Ehrlich's view of the relation of what occurs in toxin action to the course of normal physiological activity. It is not only conceivable but probable that toxin may be fixed in other cells besides those on which its activity is most manifest. This is indicated by experiments recorded by Roux and Borrel (293). These observers found that while in the case of the guinea-pig the M.L.D. was the same whether the poison was injected intracranially or subcutaneously.

in the rabbit, on the other hand, the subcutaneous M.L.D. was twenty-five times greater than the dose necessary to produce death when injected intracranially. From this, in conjunction with the above-mentioned observations of Wassermann on the possibility of fixation of toxin in the liver and spleen of the rabbit, it becomes at once obvious that we should expect such a difference of M.L.D. as Roux and Borrel have observed. We shall find immediately that these observations have another and even more important application.

In connexion with the point just discussed it may be stated that Ehrlich holds strongly that toxins differ from such poisons as alkaloids in that he has been unable to find evidence of fixation of the latter in susceptible cells. That a difference exists between the behaviour of such a toxin as that of tetanus and such an alkaloid as morphine, may be gathered from the fact that Morgenroth, in the case of the latter, could find no evidence of the formation of an antimorphine serum. It is, however, impossible at present to estimate the real significance of such an observation.

Ehrlich's View of the Nature of Antitoxins.—We have now to consider Ehrlich's attitude as to the essential nature of the antitoxin produced against a soluble toxin. His view of what may occur in the reaction of the toxin and the susceptible cell is based on the conception that possibly the reason for toxin-fixation is that toxins—as there is every reason to believe—are in constitution closely allied to some bodies which in ordinary cell-life are taken up by the cell from the surrounding lymph as food. These food-materials would contain haptophorous groups corresponding to those of toxins. What will happen during the process of immunisation, *e.g.*, of the guinea-pig against tetanus? In this animal, as we have seen, the experiments on fixation point to the conclusion that the brain-cells have more power of fixing toxin than the cells of the other organs of the body. In the process of immunisation either the amounts of toxin reacting with the brain-cells are insufficient to cause by their toxophorous groups serious interference with the cellular metabolism, or the toxoid quality of the crude toxin renders it impotent to produce harmful effects. In any case, however, it is anchored to the cell by its haptophorous groups. This anchoring is useless to the cell, for though the conception presupposes a resemblance between toxin-molecules and certain ordinary food-molecules it does not suppose that toxin can take the place of these food-molecules in the ordinary cellular metabolism. The result is that the cell is deprived of certain molecular affinities which are necessary to its ordinary vital activity. In consequence and in accordance with the general tendency of tissues to regenerate lost parts,—a view elaborated by Weigert (59),—there occurs on the part of an executive centre ("*Leistungskern*") of the cellular protoplasm (*cf.* Ehrlich (97), p. 433) a formation of fresh side-chains to take the functional place of those saturated with the useless toxin. But as during immunisation the periodically injected toxin saturates with the useless material more and more of these newly formed

side-chains the executive centre must produce more and more. Now, just as the reproductive mechanism of a cell may, when stimulated, produce new cells in great quantity, as, say, in the case of cutaneous epithelium, so the nutritive centre of the cell may be stimulated to produce the necessary side-chains. But if this happens, a point may be reached when far more side-chains are produced than are required for food-fixation. The molecules containing these side-chains are useless in the cell and are cast off into the lymph, and, finding their way into the blood, constitute the antitoxin which may be found there. The antitoxin is thus made up of the same molecular aggregates which, in virtue of their haptophorous groups, are—when these form part of the functioning protoplasm of the cell—the means by which a toxin is fixed in that cell. The difference between the haptophorous groups when functioning in cellular activity, and when in consequence of their over-production they are merely superfluous or waste material must be insisted on. In the living cell they are not acting as antitoxin, they are acting as toxin-fixatives. This difference has, according to the Ehrlich school, sometimes not been properly recognised. Thus Roux and Borrel (293) have shewn that in the intracerebral injection in rabbits of tetanus toxin there is a lowering of the M.L.D. as compared with subcutaneous injection. They considered this result to be unfavourable to the view that "free antitoxin" existed in the brain. There is no doubt that such a view is not held by Ehrlich, whose position is as we have just stated it. In this connexion reference may be made to an observation of Marie, who found that if half of the cerebral hemisphere of a rabbit were removed during life, triturated with tetanus toxin and injected into the animal from which it had been removed, tetanus did not follow. Here, if Ehrlich's view be correct, we may suppose that the death of the brain-cells which followed their removal, loosened the protoplasmic continuity of the cellular complexes and liberated the toxin-binding complexes in the form which in over-regeneration they would be cast off.

Discussion of Facts bearing on Ehrlich's View.—It will be at once apparent that this conception of the nature and origin of antitoxic bodies put forward by Ehrlich is of an extremely speculative character, and is intimately connected with the question of the ultimate molecular fabric of protoplasm. Still, there are a number of facts which may be brought forward in support of such a view. In the first place, there is a good deal of evidence for the supposition that antitoxins are formed in the fixed cells of the body. Thus Roux and Vaillard (294) have shewn that if in the course of a few days there be removed from an animal immunised against tetanus a quantity of blood equal to the total amount originally contained in the animal's body, the newly formed blood rapidly becomes as strongly antitoxic as the original blood. This is in favour of the constant passage into the circulating fluid of substances from some fixed tissue. The same conclusion is brought out in the more extended researches of Salamonsen and Madsen (300) working with goats immunised against diphtheria. These observers withdrew quantities of blood, and

restored the lost volume by injection of saline fluid. A fall in antitoxic power of the blood occurred, but this was succeeded by a rise, again shewing that the blood obtains its antitoxic constituent from outside itself. The last-named observers have noted a further fact leading to the same conclusion, namely, that the injection of pilocarpine into an animal during an immunisation will lead to an increase of antitoxin in the serum. The well-known pharmacological effect of this agent in stimulating ordinary glandular secretions has led to a comparison between glandular action and the secretion of antitoxin. Metchnikoff does not admit the extrasanguineous origin of antitoxic bodies; in a guinea-pig immunised against tetanus he caused a leucocytic exudation in the peritoneum by the injection of saline solution, and found that this exudation was much more antitoxic than the serum of the animal. Weigert's (351) criticism of this result that leucocyte-containing tissues, such as the spleen and bone-marrow, do not shew in an immune animal an apparent excess of antitoxin, does not quite meet the case; in the first place, because among the exuded leucocytes in Metchnikoff's experiment there was an excess of mononuclear cells, which are probably not produced exclusively in the marrow, nor even in the spleen; and secondly, because the fluid of the exudation is, for quantitative measurements, more comparable to the closely allied blood-serum than is any extract of a tissue, however prepared. Whilst the possible relationship of changes in the cellular content of the blood to the antitoxic capacity of the serum requires further investigation, the evidence at present rather points to an origin of antitoxins in the fixed tissues, and so far is favourable to Ehrlich's view.

Facts bearing on the Source of Antitoxin.—We must now undertake the difficult inquiry whether there is any evidence pointing to the formation of antitoxin in any particular tissue. According to Ehrlich, wherever toxin is fixed there antitoxin may be formed; and thus, as for instance in the case of immunisation of the rabbit against tetanus, to which reference has been made, it is possible that antitoxin may be formed in organs where toxin-fixation may produce little serious pathogenetic effect. There is a difficulty in connexion with the subject generally which has already been hinted at, namely, how are we to judge that an organ is specially rich in antitoxin. If the estimation is to be made per unit of mass it is evident that the proportion of inert matter is unknown. Further, if secretion takes place immediately after formation, the amount of antitoxic material present at any one time may be small, while in reality the output may be very great. The most thorough and extensive observations in this connexion have been made by Dzierzgowski, who tested the organs of horses immune against diphtheria by extracting the juices by hydraulic pressure. In this way the number of immunity-units present in an organ could be determined. He found that the kidneys, supra-renals, and some of the lymphatic glands contained the greatest amount of antitoxin. These results are in agreement with what has been observed in tetanus by Metchnikoff (232), in which case no special richness

of the susceptible central nervous system in antitoxin could be observed. There is thus no evidence available that the site of antitoxin-formation is in the organs with which toxins, such as those of diphtheria and tetanus, very probably have very great affinity. Nor is there any evidence pointing to any tissue as the special focus of formative activity. It must be remembered here that as yet nothing is known of the sources from which the fluid constituents of the blood are, under ordinary conditions, derived; nor do we know whether this information would throw light on the problem at present under consideration. We shall see later that the elucidation of the questions relating to immunity has brought to light the probability that the albuminous constituents of the plasma are of a most varied and complex character, and thus may have more than one site of formation. While we have no direct evidence of an organ susceptible to toxin being the site of antitoxin-formation, we must here consider whether certain observations of Meyer and Ransom do not rather militate against the probability of such a source of antitoxin. We have spoken of the evidence brought forward by these observers which points to the axons of the motor nerves being the paths by which tetanus toxin reaches the central nervous system. They have further observed in one experiment in which an animal was actively immunised against tetanus, and in which antitoxin had appeared in its serum that this did not prevent it succumbing to the injection of a single M.L.D. of toxin when the injection was made into a peripheral mixed nerve. It is obvious that the further investigation of this matter must be looked for with the greatest interest. Meantime, it is difficult to see how Ehrlich's view can be reconciled with this observation. According to that view in immunisation it is necessary that fresh toxin should constantly be fixed in the susceptible cells. Yet in this particular instance the placing of toxin in a situation where its fixation is especially easy, proves that the susceptibility of the cell is the same as if no immunisation-process had been practised. Again, if in tetanus the brain-cells are the sites of antitoxin-formation, one would suppose that in the experiment under consideration the toxin on being introduced into the cell would be immediately neutralised by antitoxin in process of formation. It has been pointed out (289) that if Ehrlich's view be accepted difficulties arise as to the incidents of an ordinary immunisation if, as is usual in the later stages, unaltered toxin be injected. The production of antitoxin depends on the fixation of this toxin in the cells; but if this fixation occurs, what prevents the toxophorous group of the toxin working pathogenetically in the cells? The results of Meyer and Ransom's work tend to make an answer to this question all the more necessary now.

Relation of Antitoxin-production to insusceptibility to Toxin.—We must now consider whether the development of insusceptibility in an animal cell is necessarily correlated with the capacity of antitoxin-formation in the animal of which the resistant cell is a part. Dr. Dean (78) states that in horses previously immunised against diphtheria, but in which

antitoxin-formation had been reduced to a minimum, the animals yet shewed a degree of resistance to fresh injections of toxin such as would not have occurred in untreated horses; and it has been shewn (288) that in immunising guinea-pigs against tetanus in the early stages, an animal may not have in the whole serum of its body more antitoxin than what is sufficient to neutralise a fiftieth part of the toxin which can be injected into it without any result. It is, further, the experience of workers in serum laboratories that some animals which develop a considerable power of resistance yield only a comparatively weak antitoxic serum. Then, again, an animal may go on for years yielding a powerful antitoxin, and then without shewing susceptibility to the toxin may cease to respond by furnishing an equally powerful serum. But the most striking point in this relation is the phenomenon of hypersensitiveness which has been observed by Behring (20, p. 1051) and others in animals being treated for antitoxin-production. Behring noted a horse which had been for some time immunised against tetanus and yielded a good antitoxic serum. On a fresh toxin injection being practised it suffered from severe symptoms and died. The symptoms were not those of tetanus, but consisted of fever, loss of weight, muscular tremors, and weakness. These he attributed to the tetanus toxin, itself, as antitoxin will prevent toxin causing such symptoms to appear. Similar cases have been observed in the Pasteur Institute in Paris (*v.* 237, p. 387), and Brieger (44) has noted the occurrence of death from tetanus in a horse while being immunised against tetanus and while possessing in its serum more antitoxin than was necessary to neutralise the dose of toxin which proved fatal. Again, it has been shewn by Knorr that a hypersensitiveness to tetanus can be induced in guinea-pigs by injecting ordinary toxin in very small fractions of the minimal lethal dose. In fact, Behring and Kitashima (21) found it impossible to immunise animals against tetanus by injecting ordinary toxin, however small the doses were in the first instance. All this, according to Behring, points to the view that in immunisation an injury is done to cells. Such facts, taken along with what has already been said, lead us to conclude not only that we know nothing of the site of antitoxin-production, but, further, that we must leave open the question of the identity of the capacity for the development of resistance against a toxin and of the capacity of producing antitoxin.

Notwithstanding what has been said we must admit the close parallelism which exists between the observed facts and the supposition that in antitoxin-production the constant stimulation of the animal body by toxin leads to it doing more and more work in the form of a constantly increasing amount of antitoxin-production. Thus Knorr shewed that in a horse, whose blood had for some time contained per c.c. a constant quantity of antitoxin, the injection of a single unit of toxin stimulated the production of 100,000 immunity units. It has also been shewn (288) that if immunisation against tetanus be produced, not by the injection of constantly increasing doses of toxin, but by the repeated

injection of the same amount, there is a gradual and progressive rise in the antitoxin content of the animal's blood. In such an experiment, after four doses had been administered, the animals so treated had in the whole serum of the body sufficient antitoxin to neutralise only two M.L.D. of toxin. In animals treated with double the amount of toxin, *i.e.* that contained in eight doses, the serum contained enough antitoxin to neutralise about 120 M.L.D. There was thus evidence of continued and increasing effect produced by what might be called a succession of equal stimuli. Such a result is compatible with the conception of Weigert that some constantly increasing process is going on in antitoxin-formation. This process is not indefinite in its possibilities. Dr. Dean (78) and others have shewn, as already stated, that in the immunisation of horses for the purpose of obtaining therapeutic serums a point is reached when, notwithstanding fresh doses of toxin, no increase in the antitoxic value of the serum occurs; and if the toxin injections be stopped the serum shews a constant decline in antitoxin content. Even after some years, however, the serum will still appear more antitoxic than that of the ordinary horse, and now a recommencement of toxin injection will be followed by a rapid development of antitoxin,—more rapid than would occur in a horse not previously treated. Dr. Dean points out that on Weigert's conception, increased side-chain formation will only occur so long as the executive centre of the cellular protoplasm is uninjured, and he suggests that in immunisation such an injury may really occur to a slight extent at every injection. In process of time the injury may be such that it finally interferes seriously with the vital activity of the cell, and prevents the further production of antitoxin. That injury may be done by the toxin injections carried out during an immunisation, is also borne out by an interpretation put on the result of one of their experiments by Salamonsen and Madsen (300), who noticed that after a fresh toxin injection the fall of the antitoxic value of the serum which occurred was more than could be accounted for by the mere neutralisation by the fresh toxin of antitoxin already formed. They suggested that not only did such neutralisation occur, but that there was also a temporary diminution of production of antitoxin by the active cells. Such a check to vital activity is consonant with the occurrence of a slight injury. The summation of a series of such might lead ultimately to a cessation of the capacity of the cell for continued increased antitoxin production. In this connexion the question arises whether in reality immunisation is possible without such slight injury, which in its mildest forms may be called a stimulus. In other words, if we accept Ehrlich's view of the existence of haptophorous and toxophorous groups in the toxin molecule as correct, is the mere constant saturation of side-chains in the cell, by the constant taking up of haptophorous affinities, by itself capable of causing the appearance of antitoxin in the serum? According to the hypothesis, three factors must contribute to this result—first, the fixation of the toxin; secondly, the over-production of side-chains; and thirdly, the casting off of these side-chains. If the action of the haptophorous group

alone is sufficient for the production of this result, then it ought to occur when a toxin in which the toxophorous groups have lost their activity is used. This point has been worked at by Bruck (49), who investigated a tetanus toxin which (apparently by lapse of time) had lost all its toxicity, but was still able to combine with antitoxin, as was shewn by the observation that when it was added, together with active toxin, to an otherwise neutral mixture of the latter with antitoxin, the mixture was found to be no longer neutral; that is, according to Ehrlich's phraseology, the given amount of antitoxin did not contain sufficient binding affinities to saturate both those of the non-toxic and the toxic toxin. This non-toxic toxin was used to immunise animals, but the serum of these animals did not shew any antitoxic power. In comparative experiments made with a similar toxin which, though very weak, yet shewed some toxic power, an antitoxic serum was produced. Bruck, however, obtained evidence that the non-toxic toxin was fixed in the body; thus, if it were injected one hour before one M.L.D. of active toxin, this amount of toxin was no longer sufficient to kill the test-animal. The deduction is that, as some of the toxoid was fixed in the cells, the whole of the active toxin could not now gain admission. Bruck also found what he interprets as evidence that the non-toxic toxoid stimulated the cells to produce fresh side-chains; for if the active toxin were not injected till twenty-four hours after a quantity of the non-toxic toxoid, then its M.L.D. was less than usual, that is, there was an increased susceptibility developed. Here Bruck supposes that the presence of the non-toxic toxin had stimulated the cells to form new side-chains, which, however, as they remained attached to the cell, increased its capacity for binding toxin, that is, increased its susceptibility. The view taken is that the absence of active toxophorous groups in the non-toxic toxin prevented one of their effects in the cell in the course of immunisation, namely, the loosening of the newly formed side-chains. These observations are of great interest, as shewing that in antitoxin-formations something more than the action of the haptophorous part of the molecule may be required. It may be that the toxophorous group acts as the cause of the third factor alluded to as necessary before antitoxin can appear in the serum, namely, the detachment of the side-chains from the cells. It is clear, however, that a presumed injury of this nature does not account for the evidence of more serious interference with cellular activity to which allusion has been made, namely, the arrival of a point in an immunisation when apparently the cell tends to lose its capacity of forming new side-chains. The whole question, concerned as it is with the interpretation of indirect evidence, is full of difficulty. But we must be prepared for further investigation revealing evidence of changes in the cell produced by the poisonous part of the toxin molecule.

Antitoxins in Relation to Recovery from Disease.—At the outset here it must be observed that undoubtedly ordinary animals sometimes possess in their serum substances capable of neutralising to a small degree bacterial toxins. Thus it has been shewn with regard to diphtheria

toxin by Drs. Meade Bolton, Cobbett, and others, that the serum of ordinary horses often shews a certain antitoxic quality. Similar observations have been made on tetanus toxin, and Neisser and Wechsberg (254) have shewn that in both men and horses there sometimes exists a normal antistaphylolysin. What relation these normal antitoxins bear to the antitoxins produced by immunisation is unknown. Kraus (169) found that some animals possessed a normal antitoxin towards certain vibriolysins, but he states that the normal antitoxins must, to produce an effect, be in contact with the toxin for a longer time than was necessary in the case of the immune antitoxins, and he inclines to the belief that they are distinct substances. Whether normal antitoxins may play a part in the resistance which many individuals present towards certain infections we cannot say.

With regard to the main question of the relation of ordinary immune antitoxins to disease, we must here consider two questions: first, in disease arising naturally and untreated, does the capacity of antitoxin-production play a part in recovery? secondly, what is the explanation of the undoubted therapeutic utility of such an antidote as diphtheria antitoxin? With regard to the first, it must be noted that recovery from untreated disease may simply be due to a non-fatal dose of toxin being absorbed. The bacteria [*e.g.* in diphtheria] might be killed by the bactericidal powers of the body, which we shall presently discuss, before they have secreted a fatal amount of toxin.

Comparatively little work has been done bearing on the part which the actual formation of antitoxins during an illness may play in the recovery of the affected individual. According to Abel, up to the eighth day after the commencement of an attack of diphtheria there is little evidence of antitoxin in the serum, but after that period there is often a protective power present, which may, however, disappear in a few months' time. Abel also states that in a certain number of ordinary individuals such protective powers naturally exist in the serum, and to this he attributes the non-susceptibility to the disease which often appears to exist in persons exposed to infection. Similar results have been put forward by Klemensiewicz and Escherich. Although it may be true that, during recovery from diphtheria, antitoxin is present in the blood, the subject requires further inquiry. Even if the fact be established, it by no means follows that the presence of antitoxin free in the blood-plasma is the cause of recovery. We may state it as a possibility that the antitoxin present in recovery may be a surplus production of the cells, to whose activity was due the neutralisation of the moiety of toxin which actually produced the pathogenetic effects manifested. A not unimportant point in this connexion is the prophylactic action of such an antitoxin as that of diphtheria. That such an action really exists is undoubted, and it would appear as if the manufacture of the toxin by the diphtheria bacillus was an important factor in enabling the organism to gain the capacity of multiplying on the bodily tissues.

With regard to the cause of the therapeutic action of antitoxins, it is obvious that our ignorance of the essential nature of the toxin-antitoxin reaction necessitates a most cautious statement. Antitoxin, when introduced into an individual suffering from diphtheria, will be in a position to neutralise toxin absorbed into the body from its site of formation subsequent to the antitoxin injection. Such an effect does occur, for after antitoxin is actually in the blood, very large multiples of the minimal lethal dose of a toxin can be injected into an animal without any bad results. It may be observed, parenthetically, that such an occurrence presents some difficulty, if Ehrlich's view of the production of the antibody in susceptible cells be correct; for if in an immunisation to obtain a therapeutic serum there are large quantities of antitoxin in the blood, how does any definite amount of unsaturated toxin reach the cells in which it is to stimulate the antitoxin-production?

The most important point for consideration here is, that when an animal has received a dose of a toxin which is inevitably fatal, and when sufficient time has elapsed for that toxin to be fixed in the susceptible cells, the fatal result can be prevented by the injection of antitoxin. Here, as we have seen from the experiments of Dönitz, the longer the interval elapsing between the toxin injection and the antitoxin injection the greater must be the dose of antitoxin to avert death. It is highly probable that toxin fixed in the cells must in some way have its action neutralised. In what this neutralisation consists we cannot say, but there are two main possibilities,—either the toxin is detached from the cell and carried away in a harmless combination with antitoxin, or its toxic action is neutralised. Current thought, largely in consequence of Ehrlich's hypothesis, inclines to the former view, and there is much to support such an attitude. If the toxin-antitoxin reaction be a reversible one, then the bathing of a cell, in which toxin was fixed, with antitoxin in concentrated solution would cause the equilibrium of the combination in the cell to be upset, and would lead to detachment of toxin. This would happen whatever was the affinity of the cell for the toxin, as compared with that of the antitoxin for the toxin, though, of course, if the latter affinity were less than the former, a greater excess of antitoxin would be required to detach such an amount of toxin as might be required for the prevention of death. The constant recurrence of questions affecting the dissociation of the toxin-antitoxin reaction is, as this fresh instance shews, very striking. It appears necessary to assume that it exists, and it appears equally necessary to assume that, if the occurrence does take place, it should have its limits. That it is limited in the body is rather indicated by the observation of Rehns and others that no immunity can be produced in an animal by injecting neutral mixtures of toxin and antitoxin. The discussion of any explanation which might be offered of the facts if the toxin-antitoxin is not reversible, would involve us in pure speculation. We can only say that any explanation of the toxin-antitoxin reaction must include the explanation of the undoubted therapeutic effects of antitoxic bodies. In conclusion here, we may say

that while, as we shall see later, there is direct experimental evidence of some substances analogous to toxin in composition being actually detachable from their combinations with cells, no evidence has yet been adduced of such detachability, either in toxins themselves nor in the bodies (*e.g.* complements) most closely allied to them. In fact, the available evidence is rather against such a possibility. We must, therefore, be prepared for a complete upheaval of our ideas on the whole subject.

Bactericidal Action in the Animal Body

General Facts regarding Immunity against Bacterial Invasion.—We must now consider our knowledge regarding immunity in those bacterial diseases in which the pathogenetic effects are associated with the active multiplication of bacteria within the bodily tissues, whether these effects are local or general, or first local and then general. As we have already pointed out, in discussing the general pathogenetic effects of bacteria, some organisms never pass beyond the focus of inoculation, and apparently cannot do so. The effects of these organisms are due to the elaboration of the soluble toxins, the nature of which has been discussed. Other bacteria, whether in reality they do so or not, can multiply in a widespread manner in the body. These organisms very often do not produce substances of the nature of the soluble toxins formed by the diphtheria and tetanus bacilli, though in certain cases it is probable such substances may be formed. Here the toxic pathogenetic effects are probably caused chiefly by intracellular toxins. In the cases of bacteria forming soluble poisons, if these poisons are present in the body in sufficient amount to cause death, it may be enough for the recovery of the individual that the poisons are neutralised. The bacteria cease to multiply and die. We have already referred to this in speaking of the prophylactic action of antitoxins. On the other hand, and especially in the case of bacteria capable of active multiplication in the tissues, and acting by means of intracellular poisons, the first essential to the recovery of the individual attacked may be that the bacteria should be killed,—as long as a living bacterium exists within the body it is a source of danger. This fundamental point must be borne in mind in all our discussions of immunity against the true infections, as, for convenience, infections in which there is an active proliferation of bacteria in the tissues may be called.

It may be recalled that it was against a true infection, namely, chicken cholera, that in the early part of the bacteriological era a means of establishing immunity was devised by Pasteur. This was followed by his immunisation (266) of cattle against anthrax. Since that time immunity has been produced against many such diseases. As examples may be quoted the work of Marmorek (214) on streptococcus infection, Drs. Eyre and Washbourn (118) on pneumococcus infection, Chantemesse and Widal (70), and Pfeiffer (273) on artificial typhoid in-

fection, and Sir A. E. Wright (361) on natural infection by the typhoid bacillus, Wassermann and Pfeiffer (271, 281) on cholera infection, Yersin, Calmette and Borrel (379, 380) on infection with plague. In all these cases the procedures adopted are of a similar kind, and in all cases where an immunity is developed that immunity is specific, *i.e.* is only available against the organism originating it. Immunity is obtained by employing as the immunising agent the protoplasm of the bacteria concerned. Though we shall have to consider the effects observed in certain cases by substituting substances derived from that protoplasm, it is well in the first place to confine attention to the immunising effects of the actual bodies of the organisms. Though sometimes immunisation has been commenced with small doses of a virulent culture, it is usual in the early stages to employ some means for decreasing the pathogenetic activity of the bacterial protoplasm. Sometimes this is heated and thereby killed, sometimes it is killed by chloroform vapour, sometimes living cultures whose capacities have been depressed by long-continued growth outside the animal body—so-called weak or non-virulent cultures—are employed. In the first two cases, as we have seen when speaking of intracellular toxins, we have material which has the capacity of producing disease effects—fever, wasting,—but has lost the capacity for multiplication. With regard to the last case, the explanation of weakness of virulence has still to be discussed. It is always necessary to commence with small doses of the immunising agent, and to increase the dose only with great care, especially when the injection of weak cultures is followed by the use of virulent cultures. Generally speaking, immunisation against bacterial infection is very much more difficult than the immunisations against the intoxications we have hitherto considered, and much greater care must be exercised. This is especially necessary, as apparently the efficiency of the injections in certain cases appears to depend on their producing transient disease-manifestations. A degree of immunity frequently manifests itself very soon after the commencement of the treatment. Thus amongst Wassermann's (342) experiments was one in which the injection of half the fatal dose of dead cholera-bacteria into a guinea-pig rendered it capable of supporting four days later the injection of four M.L.D. of living vibrios. To give an idea of the tolerance that may be developed in such immunisations, an experiment of Marmorek (214) may be quoted, in which a horse, commencing with a dose of ·75 c.c. of a living culture, of which ·001 killed a rabbit, could tolerate at the end of some months a dose of 40 c.c. Reckoning this progress of toleration in minimal lethal doses, it is, however, slow compared with what might be observed in immunisation against a soluble toxin.

The Development of Bactericidal Serums.—In immunity against bacterial invasion, as in the reaction against soluble toxins, changes often occur in the blood-serum of the immunised animal, and we can lay down as a thesis that, *in* certain cases *it has been shewn that the serum of an animal immunised against bacterial invasion contains substances inimical to the life of the invading bacteria, and* within limitations *these substances can be*

used for the passive immunisation of another animal against the specific bacterium which originated them.

We may illustrate this last position by an example from Marmorek's work—·2 c.c. of the serum of a horse highly immunised against the *Streptococcus pyogenes* if injected into a rabbit 12 to 18 hours before inoculation with twice the M.L.D. of living streptococci, was sufficient to protect the animal against illness. Further, the injection of the same serum 24 to 30 hours after inoculation with ordinary streptococcus cultures prevented the fatal effect which otherwise would have resulted. *Of the highest importance here is the fact that there is a limit to the number of minimal lethal doses of living cultures whose action can be neutralised by such a serum.* In this respect these antibacterial serums differ markedly from the antitoxic serums. Thus Wassermann (344), in studying the effect of a serum on the typhoid infection of guinea-pigs, found that such serum could have no protective action if more than a very few M.L.D. were administered. The limitations to which, as we shall afterwards see, the therapeutic application of this class of serums is thus subject have had the effect of directing investigation regarding antibacterial serums into strictly scientific lines. Attention has been chiefly paid, on the one hand, to the phenomena of the natural resistance to and of the recovery from this class of diseases; and, on the other, to the problems concerned in the origin of the antibacterial serums, of whose development during certain bacterial immunisations there can be no doubt.

In discussing the subject we shall first examine fully the facts known and the hypotheses held regarding the nature of these serums, and then consider the problem of cellular activities in relation to the origin and action of these serums.

We have seen that in the diseases in question there is evidence that the cellular contents of the causal bacteria are highly toxic. It is natural from what has been said regarding the action of antitoxic serums on extracellular soluble toxins, that we should inquire whether the antibacterial serums possess analogous neutralising effects on the intracellular bacterial toxins. Pfeiffer and Wassermann (281) found that this was not the case. Working on guinea-pigs with intraperitoneal injections of anticholera serum, they observed that these had no effect on the pathogenetic action of cholera vibrios killed by chloroform vapour, and likewise introduced intraperitoneally. The pathogenetic action was the same in animals treated with serum and in those untreated. Further, if the killed bacteria and the anticholera serum were left in contact for 24 hours before injection into a guinea-pig, there was no evidence of any interaction having taken place *in vitro* between the substances. Thus the serum had no neutralising effect on the intracellular poisons. What it does do when it neutralises the effects of the infection was indicated by other experiments of the observers mentioned. In one serum injection, instead of dead vibrios being injected, an equivalent amount of living vibrios were introduced. The intracellular toxin thus injected killed the animal, but

on testing the peritoneal exudation it was found that practically no living vibrios were left, though microscopically many degenerated forms could be observed to be present—chiefly within the leucocytes. Thus an antibacterial serum will only save an animal if it helps the animal to kill the infecting bacteria before these have elaborated one minimal lethal dose of the endotoxins. The general tendency of these observations is to indicate that an antibacterial serum owes its action not, as in the case of an antitoxic serum, to its capacity of neutralising the toxins produced by the bacteria, but to its power of killing the bacteria. We shall later discuss this point in detail, but meantime it is well to keep this possibility constantly in the foreground. Whether the antithesis between the neutralisation of intracellular toxins and the killing of the bacteria containing them is universally valid or not, it is certainly the case, as has been indicated, that in immunisation against true bacterial infection the essential feature is the development on the part of the immunised animal of the capacity of killing the causal bacteria of the disease against which it is being immunised. When this capacity is reflected in special properties in the animal's serum the latter is known as a *bactericidal serum* to distinguish it from serums which are merely antitoxic in quality. We have taken as an example of such a serum that which is developed in anticholera inoculations. *It is very advisable to bear in mind that in most of the work done on bactericidal serums, this serum and the antityphoid serum have been the main subjects of inquiry. Whether the facts ascertained regarding these two serums are true of other serums is open to question.*

The Pfeiffer Phenomenon.—The existence of bactericidal serums being thus established, we pass to consider certain cardinal facts observed regarding their reactions which form the basis for all the reasoning regarding their nature. The starting-point of all recent work here lies in what is known as the "Pfeiffer phenomenon." Pfeiffer (272) having immunised a guinea-pig by a culture killed with chloroform, injected intraperitoneally a quantity of living bacilli insufficient to cause death, and from time to time withdrew by capillary tubes small amounts of fluid from the peritoneum, and examined the condition of the bacteria. He found that in a comparatively short time the vibrios became motionless, swollen into round coccus-like bodies, and finally disappeared. The same sequence of events was observed when anticholera serum was introduced together with living vibrios into the peritoneal cavity of a non-immunised animal. This is the essence of the "Pfeiffer phenomenon," but the importance of the work of this observer really lies in the further observation that if the anticholera serum be heated for an hour at 60° C., it still has the protective effect when introduced with cholera vibrios into the peritoneal cavity of a non-immunised animal. This, taken along with the fact that such heated serum shewed no bactericidal action on cholera vibrios outside the body, led Pfeiffer to consider that the anticholera serum in itself did not contain the bactericidal principle whose action could be observed in the non-immunised animal, but that in it there was some principle which stimulated the production in the non-immunised animal of bacteri-

cidal substances. Following on this deduction came the epoch-making observation of Bordet (34), which must be considered as the starting-point for all recent research, and which has given the key to the true nature of bactericidal action. Bordet took the serum of a guinea-pig immunised against cholera and heated it for one hour at 58° C. He then mixed with it a little of a culture of cholera, and removing from time to time small quantities, tested them to see whether the bacteria were still alive; like Pfeiffer, he could observe no bactericidal action. He now added to the anticholera serum a little serum from a non-immunised guinea-pig (this serum also by itself had no power to kill the cholera vibrio), and he found that the mixture was strongly bactericidal. Thus in this experiment two substances were apparently necessary to produce the bactericidal effect—one in the anticholera serum and one in the serum of the non-immune animal. Neither serum alone was bactericidal, but acting together a bactericidal effect was produced. In future we shall, in describing such effects, speak of the serum from an immunised animal as "immune serum," and of the serum from a non-immunised animal as "fresh serum." Further, Bordet found that heating this fresh serum for five minutes to 55° C. destroyed its capacity of becoming, when associated with the immune serum, a bactericidal agent. The essential substance in the fresh serum was thus susceptible to a moderate degree of heat, and such substances are often thus described as "thermolabile," while the substances in immune serums, which are more resistant to heat, are often referred to as "thermostable." In the heating of the serum in Bordet's experiment, any thermolabile substance present which might have had a similar effect to that of the thermolabile substance of the fresh serum would have had its action destroyed. Another observation made with this immune serum was that its mixture with fresh serum was bactericidal only for the cholera vibrio. In other words, the action of the thermostable substance was specific. We shall find later that the inquiry whether similar specificity holds for the thermolabile body opens up a complex question. From our present standpoint the important points are, on the one hand, the existence of the two classes of bodies and the necessity for their interaction in producing a bactericidal effect, and, on the other hand, the different effects of heat upon them. The existence of similar classes of bodies with similar properties has been demonstrated in the cases of other bactericidal serums. As examples of the work done in this direction, reference may be made to the work of Wassermann (345), Ainley Walker (338), Pfeiffer and Kolle (278) on typhoid infection, and of Neisser and Wechsberg (254) on infection with the *vibrio Metchnikovi.*

As the result of the observations of Pfeiffer and Bordet a great number of investigations have been made. The objects of these researches have been, on the one hand, the correlation of the facts just described with facts already known, and, on the other, the elucidation of the problems which new results seem to open up. These researches may for convenience be classed in two groups: in the first place, those which have

to do with the nature and interactions of the thermolabile and thermostable elements in bactericidal action, and, secondly, those which have a bearing on the sources of these materials in the body, and the ultimate relation which they bear to the essential phenomena of immunity. We shall deal with these two classes of research in turn. We shall first look at the nature of the thermolabile and thermostable elements in bactericidal action and the nature of the interaction between these two elements.

Significance of Bacteriolysis.—Frequently, but probably not invariably, the destruction of a bacterium by an immune serum is associated with a swelling up and ultimate disappearance of the bacterial cell, such as was originally observed by Pfeiffer for the cholera vibrio. Pfeiffer and Kolle (278), for instance, observed this with typhoid immune serum. This phenomenon is usually referred to as bacteriolysis. Whether this bacteriolysis is the essential factor in the killing of the bacterial cells by an immune serum is a question which at present cannot be definitely answered, but the association of the two phenomena has for the following reason constituted a very important factor in the scientific investigation of the nature of the thermolabile and thermostable bodies now under consideration.

The Analogies between Bacteriolytic and Hæmolytic Serums.—Soon after his work on the bacteriolysis of the cholera vibrio by the combined efforts of heated immune serum and fresh serum, Bordet (36) pointed out the analogies between the properties of the serums of animals immunised against bacterial infection, and those of the serums of animals into which repeated doses of red blood-corpuscles from another species of animal had been injected. Thus a guinea-pig is taken and every three days 3 c.c., say, of the defibrinated blood of a rabbit is injected intraperitoneally. This is done on six occasions. The animal usually suffers little inconvenience, though if excessive doses be used at the outset it may die. At the end of this immunisation-period, as it may be called, the animal is bled and the serum separated. It is then found that this serum is able to cause a solution of the red blood-corpuscles of the rabbit. If injected into a rabbit in sufficient quantity the rabbit will die from an intravascular hæmolysis (see Bordet (38), Cantacuzène (68)), but in addition, and this is more important, the serum will cause a similar hæmolysis *in vitro.* The method is to take defibrinated blood of a rabbit and add it to ·8 per cent solution of sodium chloride in the proportion of five parts of blood in one hundred of the diluent. This 5 per cent suspension of blood is placed in quantities of, say, 10 c.c. in a series of test-tubes, small quantities of the immune serum are added, the tubes are set to stand in an incubator or water-bath at 37° C. for two hours. At the end of this time it will be found that the hæmoglobin will have dissolved out of the corpuscles into the salt solution in amount varying with the amount of serum added, and in the tubes containing the largest amount of serum the fluid will be quite clear and contain no vestige of the red cells in a formed condition. In this case the hæmolysis is complete. It

is needless to say that if a quantity of the simple suspension of corpuscles in salt solution be placed under similar conditions all that will happen (if hæmolytic bacteria be excluded) will be a sinking of the red cells to the bottom of the tube. By further investigation of this phenomenon Bordet found that the immune serum lost its hæmolytic action if heated to 55° C. for half an hour; but if to this heated serum there be added a small quantity of the serum of a "fresh" guinea-pig (which in itself has no hæmolytic action on rabbit's corpuscles) then the combined action of the two serums was to produce hæmolysis, just as happened in similar circumstances with cholera immune serum. Further, it was found that the immune serum produced by the injection of rabbit's corpuscles into the guinea-pig was almost if not entirely specific, *i.e.* the guinea-pig serum had little or no effect on the corpuscles of other animal species. This discovery by Bordet of the possibility of obtaining serums having lytic actions on red blood-corpuscles similar to the lytic actions of bactericidal serums on bacteria, placed in the hands of investigators a method of the greatest importance for examining the nature of the interactions of the thermolabile and thermostable bodies. The number of hæmolytic immune serums obtainable is very great. Further, as the experiments are done *in vitro*, and are completed in a few hours, results can be quickly obtained, and the exactitude with which quantities of the substances employed can be measured adds to the validity of any deductions drawn. As a result a very great mass of work has been done on the nature of the reactions of the bodies concerned in hæmolysis, and it is necessary for us to consider at some length the questions raised in the researches in which this work is detailed. *It is well to remember that the chief justification for the labour that has been expended in investigating the phenomena of hæmolytic serums lies in the analogy, which from the point of view of immunity, the fundamental facts bear to the facts known regarding bacteriolytic and bactericidal serums.*

Terminology.—At the outset it will be well to add to the terminology already used regarding the bacteriolytic and hæmolytic serums. We have defined the terms "immune serum" and "fresh serum." We must recognise the terms which are employed to particularise the thermostable and thermolabile substances occurring in connexion with these serums. The thermostable element, which is the specific substance of the immune serum, i.e. *that element which the process of immunisation adds to the ordinary constituents of the serum of the animal immunised*, is usually called in this country and Germany the "immune body," or (from Ehrlich's view of its constitution) "amboceptor"; in France it is sometimes known as the "*fixateur*" or "*la substance sensibilisatrice.*" The thermolabile body which occurs in immune serum is *merely a body present in the ordinary serum of a "fresh,"* i.e. *non-immunised animal.* It is called in this country and Germany "complement," occasionally "addiment"; in France it is frequently referred to as the "*alexin.*" It cannot be too emphatically insisted on that the amount of complement in an immune serum is either not at all increased during the immunisation process, or at any rate does

not occur in amounts to any extent greater than what may occur in ordinary serum. This statement was originally made by v. Dungern (92), and is generally accepted. Dr. Ainley Walker (338) has, however, pointed out there was a rise in complement during immunisation in the cases investigated by v. Dungern. There is no doubt that the question of the variations in complement which are observable both in health and during immunisation requires further study. It is certainly true that if any increase of complement does take place in the latter contingency the total amount is not proportional to the amount of immune body which appears in the serum even after a very short immunisation.

Unheated immune serum thus contains immune body and complement. Heating the serum to about 55° C. for half an hour destroys the action of the complement and leaves in the immune serum only the "immune body." "Fresh serum" contains only "complement," which can have its action destroyed by heat as before. Heated immune serum is commonly spoken of as serum "inactivated by heat," and when complement is added to such a serum the latter is said to be "activated" or "reactivated" by the addition of such and such complement.

Ehrlich's Work on Hæmolytic Serums.—The chief workers in connexion with the nature of hæmolytic action and of the relationship of immune body and complement are Ehrlich and Morgenroth (108). Their view is an extension of Ehrlich's conception as to the constitution of soluble toxins. Briefly stated it is this: in an immune serum the complement is the essential factor causing that change in the behaviour of the protoplasm of the red cells which results in the liberation of the hæmoglobin and swelling of the protoplasm called hæmolysis. The complement does so in virtue of possessing a molecular affinity which we must look on as analogous to or as corresponding to the toxophorous affinity of the toxin. Further, the complement has a second affinity corresponding to the haptophorous affinity of the toxin molecule. This haptophorous affinity, however, does not correspond to, and cannot be saturated by, any affinity in the protoplasm of the red corpuscles. It is here that the immune body plays its part. The immune body has no hæmolytic effect on the red cells. But in it are two haptophorous affinities; one of these can link on to corresponding affinities in the cellular protoplasm, while the other can saturate the haptophorous affinity of complement. In this way through the intermediary of immune body complement can become attached to a red cell, and once attached the actively hæmolytic affinity can exert its action in causing solution of the cellular continuity.

We shall describe the fundamental experiment on which this view is based. An immune serum capable of dissolving sheep's corpuscles was obtained by injecting sheep's blood into a goat. A quantity of this serum inactivated by heat was mixed with a suspension of sheep's corpuscles and placed at 40° C. for 15 minutes. The mixture was centrifuged and the corpuscles were in this way precipitated from the fluid in which they were suspended. By decanting this fluid off the

precipitate, the fluid and corpuscular elements present in the original mixture could be easily separated from one another. Each part was then tested with the object of finding whether anything had happened to the immune body of the inactivated serum during the time it had been in contact with the corpuscles, and especially to find whether any reaction had taken place between the immune body and the corpuscles. This could be easily done by taking advantage of the fact that for this, as for any hæmolysis by a serum, three factors are necessary: in the first place the appropriate corpuscles, secondly the appropriate immune body, thirdly complement. The presence of any two of these factors can be detected by supplying the third,—the presence of any one by supplying the other two. First, in the experiment under review, the decanted fluid was examined. Clearly the only factor of this particular hæmolysis investigated which could possibly be present in it was immune body. Therefore to test this, it was only necessary to add some sheep's corpuscles and some fresh — *i.e.* complement-containing — goat's serum. If immune body were present the corpuscles would be hæmolysed. As a matter of fact no hæmolysis occurred. Therefore the immune body had disappeared from the fluid part of the mixture. Had it become attached to the corpuscles of the original mixture now in the centrifuged precipitate? Here there might be present two elements, namely, the corpuscles and the immune body. To test this it was only necessary to add complement. The precipitate was therefore now taken, stirred up in a little normal saline solution, and some fresh goat's serum added, and the mixture placed at 40° C. for two hours. At the end of this time hæmolysis had occurred. Thus, during the time when the original corpuscles had stood in contact with immune body, they had taken up the latter from the fluid in which they were suspended. The next point was to find what would happen if to sheep's corpuscles, goat's complement alone were added. This will not by itself cause hæmolysis, but it might none the less interact with the corpuscular protoplasm. A mixture of sheep's corpuscles and fresh goat's serum was therefore made and allowed to stand for 15 minutes at 40° C. By centrifugalisation and decanting, the corpuscles and fluid were separated as before. To the fluid, sheep's corpuscles and inactivated goat's immune serum were added, and hæmolysis of the added corpuscles occurred. To the precipitate of the original corpuscles (which would have contained complement if union between complement and the corpuscular protoplasm had occurred) there was added inactivated immune serum,—no hæmolysis occurred. From this it was deduced that during the time the original corpuscles had been in contact with the complement present in the fluid in which they had been suspended, no union between these corpuscles and the complement had taken place. The following scheme of these two experiments gives at a glance the process of inquiry and the result :—

SCHEME OF EHRLICH'S FUNDAMENTAL HÆMOLYTIC EXPERIMENT

MIXTURE A.

Containing (1) 4 c.c. 5 per cent suspension of sheep's blood in ·75 per cent NaCl;
(2) 1 c.c. inactivated goat's serum;
was left at 40° C. *for* 15 *minutes,*
was then centrifuged and the fluid (A1) *decanted off the precipitated corpuscles* (A2).

A1	A2
containing fluid of A.	containing corpuscles of A.
There was added	*There was added*
(1) ·2 c.c. ordinary sheep's blood,	(1) 4 c.c. of ·75 per cent NaCl solution,
(2) ·8 c.c. fresh goat's serum,	(2) ·8 c.c. fresh goat's serum,
and the mixture was placed at 37° C. *for* 2 *hours.*	*and the mixture was placed at* 37° C. *for* 2 *hours.*
Result: NO HÆMOLYSIS of corpuscles in the ·2 c.c. of sheep's blood added.	Result: HÆMOLYSIS of corpuscles originally placed in A.

MIXTURE B.

Containing (1) 4 c.c. 5 per cent suspension of sheep's blood in ·75 per cent NaCl;
(2) ·8 c.c. fresh goat's serum;
was left at 40° C. *for* 15 *minutes,*
was then centrifuged and the fluid (B1) *decanted off the precipitated corpuscles* (B2).

B1	B2
containing fluid of B.	containing corpuscles of B.
There was added	*There was added*
(1) ·2 c.c. ordinary sheep's blood,	(1) 4 c.c. of ·75 per cent NaCl solution,
(2) 1 c.c. inactivated goat's immune serum,	(2) 1 c.c. inactivated goat's immune serum,
and the mixture was placed at 37° C. *for* 2 *hours.*	*and the mixture was placed at* 37° C. *for* 2 *hours.*
Result: HÆMOLYSIS of the corpuscles in the ·2 c.c. of sheep's blood added.	Result: NO HÆMOLYSIS of the corpuscles originally placed in B.

This experiment has been described in detail not only for its fundamental importance, but because it illustrates the method of practically

all the subsequent researches along similar lines. Almost the only elaboration which is now practised is, that whenever the taking up of any body by red corpuscles is suspected, the centrifuged deposit is, after decantation of the fluid, mixed up with salt solution, thoroughly shaken, and again centrifuged and the solution decanted; in fact, this procedure is usually practised several times to ensure that all the original fluid is thoroughly washed off the corpuscles. When "washed corpuscles" are spoken of, it is this manipulation which is referred to.

The interpretation put by Ehrlich on these two experiments was, as we have said, that complement could not combine with corpuscles while immune body could, but that when corpuscles had immune body attached to them, then complement could combine with the combination and cause hæmolysis. The next point investigated by Ehrlich was whether in an immune serum the complement and immune body present were free from each other. To test this, the exact amount of immune body and complement necessary for complete hæmolysis of a given quantity of sheep's corpuscles was determined. It was found that for hæmolysis of 5 c.c. of the 5 per cent sheep's blood emulsion in 1½ to 2 hours, 1·0 to 1·3 c.c. of inactivated immune serum and ·5 c.c. normal goat's serum were necessary. Taking advantage of the fact that hæmolysis does not take place below 3° C., such a mixture was made up below this temperature, kept at it for a time, and then centrifuged and tested as before. It was found that the immune body was attached to the corpuscles, while the complement remained free in the fluid. From this it was deduced that at the temperature named, immune body and complement could exist side by side in a separate condition. At higher temperatures there was evidence of the possibility of their entering into a loose, easily dissociable combination, and the general conclusion was drawn from all the experiments, that of the two haptophorous groups supposed to exist in the immune body, one had a strong affinity for certain combinations in the susceptible cells, while that which combined with the haptophore group present in complement was not so strong.

The Occurrence of Hæmolysins in Normal Serums.—That the development of hæmolytic serums is closely related to some normal process common in the ordinary metabolism of the animal body is indicated by the fact that the serums of some animals are naturally possessed of the capacity of hæmolysing the blood-corpuscles of other species, and there is evidence that the process of hæmolysis is in such cases identical with what takes place when in an animal a hæmolytic serum is developed by an immunisation procedure. In natural hæmolytic serums there is evidence that two bodies are concerned. Thus, Ehrlich found that the serum of an ordinary goat is hæmolytic towards the corpuscles of both the rabbit and the guinea-pig. The goat's serum can be inactivated by heat just as an ordinary immune serum can. It can be reactivated by the addition of some ordinary horse's serum, which in itself has no hæmolytic effect on the corpuscles in question. The horse's serum loses its reactivating power on heating at 55° C. From this Ehrlich deduces that the hæmolytic

action of the goat's serum is due to the presence of two substances, a thermostable and a thermolabile. The place of the latter can be taken by a similarly thermolabile body existing in the horse's serum. The thermostable body corresponds to the immune body of an immune serum, the thermolabile is a complementary body. To these thermostable bodies of normal serums Ehrlich gives the name "*zwischenkörper*." A great many examples of such bodies probably exist, but the facts are difficult to demonstrate. Rigid proof is only possible when, as in the case cited, the *zwischenkörper* is capable of being complemented by a serum in itself not hæmolytic for the corpuscles sensitive to that *zwischenkörper*.

The fact that in the case of each immune serum the action is specific for the corpuscles which stimulated its origin, prepares us to expect that the animal body is capable of giving rise to a great many bodies of the same order but manifesting individual differences, and there is abundant evidence that this is the case.

The Multiplicity of Immune Bodies and of Complements.—The first point to be illustrated here is the multiplicity of *zwischenkörper* which may exist in the same blood. To shew this Ehrlich took the serum of the goat, which, as has been said, is under normal conditions hæmolytic both for rabbit's and guinea-pig's corpuscles; it can be inactivated by heat, and, as already stated, can be complemented by ordinary horse-serum. The problem of whether it was the same *zwischenkörper* in the goat's serum which was concerned in the solution of both kinds of susceptible corpuscles was attacked. To this end there was determined the amount of inactivated goat's serum which, when activated by horse complement, was necessary to dissolve a given amount of rabbit's blood. To such a given quantity of rabbit's blood the necessary amount of inactivated goat's serum was added, and after allowing time for the corpuscles to take up the immune body the mixture was centrifuged. The fixation of the immune body was proved by the fact that the addition, to the decanted clear fluid, of rabbit's blood and horse complement was not followed by hæmolysis of the newly added rabbit's corpuscles, and by the further fact that the addition of horse complement to the centrifuge deposit caused hæmolysis of the original corpuscles. On the other hand, if to the clear fluid, instead of rabbit's corpuscles and horse complement, there were added guinea-pig's blood and horse complement, then solution of the guinea-pig's corpuscles took place. This shewed, according to Ehrlich's view, that after the rabbit's corpuscles had taken from the goat's serum all the *zwischenkörper* they were capable of fixing, there still remained a *zwischenkörper* which could be taken up by the guinea-pig's corpuscles; in other words, in the normal serum of the goat there are present, so far as the reaction under consideration is concerned, two *zwischenkörper*—one of which can act on rabbit's blood, the other on guinea-pig's blood.

Ehrlich next asked whether in the ordinary double hæmolytic action of the goat's serum the two *zwischenkörper* were complemented by the same complement. Goat's serum was filtered through a

porcelain filter, and it was found that while the filtrate was as powerfully hæmolytic for guinea-pig's blood as the original serum, the hæmolytic action on rabbit's blood shewed great weakening. This might have been due to a keeping back of rabbit *zwischenkörper*, of complement, or of both. That the *zwischenkörper* passed through in sufficient quantity was shewn by the fact that the addition of horse complement restored to the filtrate its normal capacity of dissolving rabbit's corpuscles. From this Ehrlich concludes that in the goat's serum the two *zwischenkörper* we are dealing with are not complemented by the same complement.

The multiplicity of *zwischenkörper* and the complexity of the whole reaction are borne out by Ehrlich's observations pointing to the existence of more than one *zwischenkörper* with similar effects in the same serum. Thus the serum of the dog is hæmolytic towards guinea-pig corpuscles, and when inactivated can be complemented by guinea-pig serum. By careful experimentation it was found that inactivated serum could also be complemented by horse serum, but that when inactivated serum was thus complemented it had only one-sixth of the hæmolytic action of the ordinary active serum; in other words, only one-sixth of the *zwischenkörper* of the dog serum had an affinity for horse complement, the other five-sixths manifested the affinity for the complement of guinea-pig serum. Ehrlich also adduced observations to shew that in immune serums a similar multiplicity of similarly acting immune bodies differently complemented might occur, and in a later paper with Sachs (112), he has brought forward further evidence bearing on the multiplicity of complements. He observed that normal goat's serum complemented the following mixtures:—(*a*) Guinea-pig corpuscles + inactive normal goat-serum; (*b*) rabbit's corpuscles + inactive normal goat-serum; (*c*) rabbit's corpuscles + inactive serum of goat immunised with rabbit's corpuscles; (*d*) ox corpuscles + inactive serum of goat immunised with ox-blood; (*e*) dog's corpuscles + inactive serum of goat immunised with dog-blood. Evidence could be adduced that different complements were concerned in each case. In digesting the complementing serum with papain, it was found that at a time when four complements had almost entirely disappeared one was not much affected. Treatment with soda solution caused the production of a similar effect. It was further observed that the complements present manifested different degrees of susceptibility to heat. These results might, however, conceivably have been due to a peculiar constitution of the complementary substance, and would be explicable if the latter were supposed to have a single affinity by which it could link on to many immune bodies, while, on the other hand, it possessed a great variety of affinities to which the cytolytic action was due. To meet such an objection Ehrlich tried to remove some of the complements by treating the serum with corpuscles sensitised by appropriate immune bodies, and in this he succeeded. By such treatment, while some of the complements were unaffected, a disappearance of others was observed. It may

be mentioned here that the experiments relating to the different effect of heat on different complements are of great importance, as numerous investigations have shewn that examples of such an occurrence are very frequently met with. The temperature of 55° C., at which the weakening of complementary power is usually said to be manifested, is a rough average only.

The Occurrence of Anticomplements.—The analogy existing between the action of complements and that of soluble bacterial toxins will have struck the reader. Looking at their similarity from his point of view Ehrlich would say that in both there is a haptophorous group; in both there is a group responsible for the specific action of the body. The difference lies in the fact that in the toxin the haptophorous group is linked to the cell on which the toxophorous group acts, while in the other it is linked to an intermediary body which in turn is linked to the susceptible cell. It is thus not surprising that Ehrlich should have inquired whether by injecting complement any body corresponding to an antitoxin could be obtained. Evidence exists that in many cases an anticomplementary action can be developed. Thus, ordinary horse serum complements a great number of *zwischenkörper*. If it be injected after the manner of an immunisation into a goat the serum of the latter contains the antagonising substance. To prove this, rabbit's blood is treated with inactivated goat-serum (which, as stated above, contains an immune body capable along with horse complement of causing hæmolysis), and centrifuged, washed, and mixed with salt solution. If now horse complement, along with the anticomplementary serum, be added to the sensitised corpuscles no hæmolysis occurs. That this is not due to any interaction between the sensitised corpuscles and the complement and anticomplement is shewn by the fact that if the mixture be again centrifuged, the corpuscles washed, and treated with fresh horse-serum, hæmolysis occurs. According to Ehrlich the anticomplement has protected the sensitised corpuscles by combining with the haptophorous group of the complement, just as antitoxin unites with toxin.

The Occurrence of Anti-immune Bodies.—Further, Ehrlich (110) has brought forward facts to prove that not only anticomplements but anti-immune bodies can be developed. It is plain that theoretically the action of an immune body can be inhibited by interference either with its cytophilic or with its complementophilic affinity. First, with regard to the cytophilic affinity, *i.e.* that by which it is anchored to the "receptor" of the cell (as Ehrlich calls the affinity in the cell to which a foreign substance may be anchored), Ehrlich injected into a goat the heated serum of rabbits in which an immune serum against ox-blood had been developed. He mixed a moiety of this goat's serum (heated) with varying amounts of rabbit's immune body and ox-corpuscles, allowed the mixtures to remain in contact, centrifuged off the fluid, and added a sufficient complement. The result was that several multiples of the simple dissolving dose of immune body were required before there was any evidence of blood-corpuscles, immune body, and complement uniting. This

is certainly evidence of an anti-immune body acting on the cytophilic affinity of the immune body, provided that the corpuscles in the case in question were not, as we shall see often occurs, capable of fixing many times the amount of immune body requisite for simple solution. In this latter event the corpuscles might attach to themselves a considerable amount of immune body with anti-immune body anchored to its complementophilic affinity, and there might still be room for a simple dissolving dose to be present in addition. Bordet (41) has brought forward experiments which according to Ehrlich and Sachs (114) point to the existence of anti-immune bodies which link themselves to the complementophilic affinity. Working with the serum of rabbits immunised with ox-blood, he found evidence that the action of the immune body it contained was antagonised by the heated serum of guinea-pigs which had been injected with the serum of fresh rabbits. This last serum contained naturally no *zwischenkörper*, so that the development of antiamboceptors by its use must have resulted from the action of other molecular complexes. Ox corpuscles sensitised with rabbit's immune body were washed and the anti-immune body was then left in contact with them. The corpuscles were again washed; on a suitable complement being added hæmolysis took place. Whether further research will substantiate these views as to the action of anti-immune bodies or not, there can be no doubt from such experiments as those of Bordet, Müller, and others, that substances of this nature exist.

The Occurrence of Complementoids.—Just as from toxins weaker bodies, the toxoids, can be formed, so from complements there is evidence that weakened bodies, or complementoids, can be produced, though, so far as is known, these are not quite analogous to the toxoids in the relation of their properties to those of the parent substance. Ehrlich obtained evidence of their existence by injecting complement inactivated by heat into an animal. In the serum of this animal it was found that, following on these injections, an anticomplement appeared. The deduction from this was that while, in consequence of heating, the cytotoxic property of the complement had disappeared, its combining affinity was still intact and could stimulate the production of an antibody. The complementoid differed from a toxoid in that while toxoid can partially saturate antitoxin, no evidence could be obtained of complementoid partially saturating immune body.

Such are Ehrlich's main positions. From considerations of space it is quite impossible to enter fully into the minute details of his work. A few points, however, deserve attention. For instance, in the case of many of the substances dealt with, while definite and independent linkings appear to exist in a molecule, it does not follow that the independence of these linkings is absolute, *e.g.* that the saturation of one link or affinity leaves the others in their original condition. Thus, when the cytophilic group of an immune body is anchored, the complementophilic group often has its avidity for complement raised. This is manifest in the fundamental experiment, from which it appears that

immune body and complement exist side by side in the serum till the immune body becomes attached to a cell, when at once its other affinity takes up complements. Again, Ehrlich and Sachs (113) have shewn that occasionally when the activity of the cytolytic group of the complement molecule is affected by heat (complementoid), the avidity of the haptophorous group is increased. Taking into consideration the close affinities between complement and simple toxins, this may be taken as furnishing an experimental justification for Ehrlich's view that in toxoid development one possible toxoid (protoxoid) may exist in which, while the potency of the toxophorous group is diminished, that of the haptophorous group is increased. In connexion with this hæmolytic work a final point may be mentioned. The development of a hæmolytic serum by an animal species A when the blood of a species B is injected is common. The development of a hæmolytic serum when the blood of one individual of species A is injected into another individual of the same species occurs, though not constantly; such a hæmolysin is called by Ehrlich (111) an isolysin. The development of a hæmolysin by the injection of an animal with its own blood is excessively rare. This non-development of an autolysin is an expression of what Ehrlich calls the "*horror autotoxicus*," which dominates an animal organism.

Results bearing on Ehrlich's Work on Hæmolytic Serums.—Having hitherto given Ehrlich's views without reference to criticism they have provoked, or to the results of other observers, we must now consider some of the objections which may be urged against them, and especially here Bordet's work (38). In Ehrlich's view it is evident there is supposed to be a fixed relation between immune body and complement. If a substance unites molecularly with another substance, it is plain that the union will take place in definite proportions. A certain amount of immune body cannot take up more complement than it has complementophilic affinities for. When all the available affinities of the immune body are satisfied, then so far as the possibility of any hæmolytic action occurring is concerned any additional complement present is an inert body. Further, Ehrlich holds to the probability of many complementary bodies existing side by side in the normal serum. The different immune bodies of different specific immune serums may act in combination with different complements. On these two points—rigidity of molecular relationship between immune body and complement and multiplicity of complementary bodies—Bordet joins issue with Ehrlich. It may be said, however, that, generally speaking, he has independently arrived at the same conclusion as Ehrlich on many of the chief points regarding hæmolytic serums, as, for instance, the fixation of immune body to the sensitive cells, and he has made many valuable additions to our knowledge of the subject. Amongst other contributions to the investigation, he has shewn that it is to the stroma of the red blood-corpuscle that immune body becomes attached, and, further, that by the injection of stromata into an animal there can be obtained a serum hæmolytic to the corpuscles from which the material

injected was derived. Of his objections to Ehrlich's interpretation based on the main facts, about which both observers are in the main in agreement, we shall first take up the question of singleness of complement. The French school generally has been much impressed with the fact that the thermolabile nature of complementary serums recalls the similar behaviour towards heat shewn by many ordinary ferments, and it is natural that this resemblance should suggest the possibility of complements possessing the general quality of ferments for originating changes of indefinite extent. We shall, in fact, see later that the complements or alexins are often included by French writers in a general group of substances named cytases, a word framed on the model of the general terminology applied to ferments. Seeing that solution of continuity of cells analogous to peptic digestion is a common feature of alexin action, it is perhaps not surprising that the possibility of only one substance being concerned in the process should be contemplated. Bordet founds his view of the singleness of complement or alexin on an extension of Ehrlich's observation that an immune body can be complemented by more than one kind of serum. He notes that a hæmolytic serum produced by injecting rabbit's blood into the guinea-pig can be complemented not only by guinea-pig serum but by that of the rat, the goat, the dog, and even the pigeon. Further, a serum produced by injecting cholera vibrios into the goat can be complemented not only by the serum of the goat but also by that of man, of the guinea-pig, the rabbit, the rat, the fowl, and the pigeon. He further produces evidence that the alexin which dissolves cholera vibrios is the same as that which dissolves red blood-corpuscles. At the same time, he does not adhere to a rigid view that there exists only one complementary body acting through all possible immune bodies. The following is a scheme of his fundamental experiment:—

Scheme of Bordet's Experiment to shew Identity of Bacteriolytic and Hæmolytic Alexins

Materials used—

(1) *Emulsion of cholera vibrios.*—A 24-hour agar culture of the cholera vibrio suspended in 5 c.c. of ·65 per cent NaCl.

(2) *Inactivated cholera serum.*—The heated serum of a rabbit immunised with the cholera vibrio.

(3) *Heated fresh rabbit-serum.*—Heated serum of fresh rabbit for purpose of comparison.

(4) *Fresh guinea-pig serum.*

(5) *Sensitised rabbit corpuscles.*—Washed corpuscles from two drops of rabbit blood sensitised by action of ·2 c.c. inactivated serum of guinea-pig immunised with rabbit blood.

Stage 1. *The following mixtures were made—*

Mixture A.	Mixture B.	Mixture C.
(1) ·5 c.c. fresh guinea-pig serum.	(1) ·5 c.c. fresh guinea-pig serum.	(1) ·5 c.c. fresh guinea-pig serum.
(2) ·3 c.c. inactivated cholera serum (rabbit).	(2) ·3 c.c. heated fresh rabbit serum.	(2) ·3 c.c. heated fresh rabbit serum.
(3) ·5 c.c. emulsion of cholera vibrios.	(3) ·5 c.c. emulsion of cholera vibrios.	

Stage 2. *The three mixtures are allowed to stand* 1 *hour and there was then added—*

(4) ·2 c.c. sensitised rabbit corpuscles.	(4) ·2 c.c. sensitised rabbit corpuscles.	(3) ·2 c.c. sensitised rabbit corpuscles.
Result.	*Result.*	*Result.*
No hæmolysis of sensitised rabbit corpuscles.	Hæmolysis of sensitised rabbit corpuscles.	Hæmolysis of sensitised rabbit corpuscles.

It will be observed that in the first stage of the experiment only in mixture A were there the two elements (viz. cholera vibrios and inactivated cholera serum) capable of removing alexin from the fresh guinea-pig serum; and in the second stage of the experiment only in A was there evidence of the absence of alexin. Bordet with Gengou (43) has performed other experiments on the same lines to shew that plague bacilli sensitised with an antiplague serum could take up the same complement as rabbit corpuscles sensitised by an antirabbit immune serum. The general interpretation is the same as in the experiment detailed. The view of Ehrlich that a cell will not take up complement unless immune body be present is confirmed, but, as in the other experiment, evidence is recognised of one complementary body acting along with two immune bodies.

To turn now to Bordet's objection to the existence in hæmolysis of a definite quantitative relationship between immune body and complement. This is chiefly founded on the following experiment. It was found that ·4 c.c. of a hæmolytic serum would dissolve the corpuscles of ·5 c.c. of blood in one hour; but if, instead of adding this amount of blood to the serum all at once, it was added fractionally, a different result was obtained. Thus to the ·4 c.c. of serum ·2 c.c. of blood was added, and an hour later ·1 c.c. and so on. It was found that though the first fraction was dissolved the later fractions were not. The first fraction had apparently used up all the hæmolytic agent. Bordet compares what has occurred with what may be observed to take place with filter-paper and a weak solution of, say, methyl-violet. In such a solution there may be enough stain to colour a large piece of filter-paper a uniform tint, but if the filter-paper be not put into the solution whole but in successive pieces, the pieces put in first will be stained much more deeply than those put in later, and the last fragments may hardly be coloured at all. Bordet

interprets the experiment as shewing that there is not a definite relationship between a given amount of red corpuscles and a given amount of immune body and complement, but that the corpuscles can take up varying amounts of the substances according to the amount they are brought in contact with. He looks upon the action of the immune body as a sensitisation of the cells to the action of the cytolytic complement, and hence gives the name of *sensibilisatrice* to it. Bordet has brought forward further experiments in support of his view of the absence of specific molecular relationships in the hæmolytic reaction. He states that the serum produced by injecting rabbit corpuscles into the guinea-pig can, when inactivated, be reactivated not only with fresh guinea-pig serum, but also with fresh rabbit-serum. If the serum be introduced into a rabbit, an antiserum which contains a small amount of anti-immune body and a large amount of anticomplement, can be obtained. This anticomplement can, in the hæmolytic reaction, neutralise the guinea-pig complement but not the rabbit complement. Bordet deduces from this that these two complements must therefore differ from one another in what Ehrlich would call their binding affinities. But if this be so, how, he asks, can there be a molecular relationship between this binding group and the haptophorous group in the immune body, seeing that when the corpuscles are treated with immune body either complement can gain admission to these corpuscles and effect their solution? To this deduction Ehrlich, who has repeated the experiment, replies by saying that it would only be cogent if there were one immune body present in the immune serum. He brings forward evidence that in the serum there are really two immune bodies, and that one can be complemented by guinea-pig, the other by rabbit complement. He also replies to Bordet's criticism that different results are obtained when to the amount of immune serum capable of dissolving a given amount of blood, the blood is added in fractions instead of all at once. He repeated Bordet's experiment with a slight variation. An immune serum was obtained from a goat injected with dog's blood. This serum could, when inactivated, be reactivated either with fresh goat- or sheep-serum. The exact amount of serum was determined which with the minimum amount of complement would hæmolyse 2 c.c. of a 5 per cent solution of dog's corpuscles. To each of a series of tubes containing this amount of the suspension of dog's blood there was added a multiple of the amount of inactivated immune serum necessary for simple solution. The multiples used were $1\frac{1}{4}$, $1\frac{1}{2}$, $1\frac{3}{4}$, 2, $2\frac{1}{2}$, and so on. The mixtures were allowed to stand for an hour to enable the corpuscles to take up immune body. It is evident that if the corpuscles do not take up more immune body than is absolutely necessary for their solution, then in the tube containing twice the simple dissolving dose, there ought to be a dissolving dose free. After standing, the tubes were centrifuged and the decanted fluid tested for the presence of free immune body. This was done by adding the test-dose of dog's corpuscles along with sufficient complement. It was found that only in the tubes containing more

than twice the simple dissolving dose was there complete hæmolysis of the new blood added. This was not, however, true of all similar cases examined. Thus in the case of an immune serum produced in the rabbit by injecting goat's corpuscles and complemented with guinea-pig serum, it was not till a hundred times the simple dissolving dose of serum had been added to the test-amount of blood that evidence of one free dose of immune body was obtained. Ehrlich explains this result, and also that of Bordet with fractional amounts of blood, by supposing that in the red corpuscle, beside the side-chains, on whose integrity the holding together of the protoplasm depends, there are others concerned in other protoplasmic functions which still can fix immune body. It is evident that this interpretation depends for its validity on the assumption that the hæmolytic binding receptors have a greater affinity for immune body than the other receptors capable of binding the latter. Otherwise there could be no determination of the minimal dissolving dose of immune body, apart from the maximum amount of immune body which the cells could take up without any immune body being left free in the serum. With regard to these experiments it may be said that on Ehrlich's views the complexity of the substances involved is very great. Thus, further to meet Bordet's criticisms, he has, along with Marshall (106*a*), brought forward evidence which he interprets as shewing that besides the possibility of red corpuscles taking up more immune body than is necessary for simple solution, there is also the possibility that one immune body may take up more than one complement. The complement which actually causes the hæmolysis he denominates the dominant complement, the others being merely fixed on the immune body and probably taking no part in the reaction.

Ehrlich's results regarding a blood-corpuscle taking up more immune body than the simple hæmolysing dose, have formed the starting-point for the investigations of Prof. Muir (251) (alone, and also with his pupil Browning) on the nature of hæmolytic action and the properties of immune body and complement. In the course of this work many new points have been disclosed, and Ehrlich's observation of the taking up by red corpuscles of more immune body than is necessary for hæmolysis has been amply confirmed. But here the further important point has been established, viz. that if the corpuscles which have anchored the immune body to saturation be centrifuged, washed, and brought into contact with fresh corpuscles, the excess of immune body dissociates and attaches itself to these fresh corpuscles which can now be hæmolysed. As this experiment illustrates the method of investigation it may be detailed :—

[Table.

Tube A

Contains—

1 c.c. of 5 per cent suspension of ox corpuscles.

Add—

Excess (20 doses) of immune body from rabbit immune serum.

Stand at 37° C. for 1 hour.

Centrifuge and wash with salt solution.

Add—

1 c.c. suspension of untreated ox corpuscles.

Centrifuge to bring corpuscles in contact.

Stand at 37° for 1 hour.

Shake up and add—

·2 c.c. (more than two doses) of guinea-pig complement.

Stand at 37° C. for 1 hour.

Result—

Hæmolysis of all corpuscles.

Tube B

Contains—

The same as A.

Add—

The same as A.

Stand at 37° C. for 1 hour.

Centrifuge and wash with salt solution.

Add—

1 c.c. suspension of untreated ox corpuscles, and

·2 c.c. guinea-pig complement.

Stand at 37° C. for 1 hour.

Result—

Added corpuscles remain practically intact.

This result has also been obtained by Morgenroth (245). Prof. Muir further found that when red cells were saturated with immune body and then hæmolysed by a minimum amount of complement, the superfluous immune body was not destroyed but remained linked to the remains of the protoplasm in the fluid. This was shewn by the observation that if fresh red blood-corpuscles were placed in such a fluid *at 0° C.*, then separated and washed, no trace of their having taken up immune body could be obtained. If immune body had been free in the fluid we know from Ehrlich's fundamental experiments (*vide* p. 99) that the corpuscles would have taken it up at this temperature. When, however, the fluid to which the fresh corpuscles had been added was kept *at 37° C.* for an hour, the corpuscles when separated and washed were found to have taken up immune body. Prof. Muir concludes that at the higher temperature dissociation of immune body from its protoplasmic combination was effected just as would happen with unhæmolysed corpuscles. We can only give a brief outline of Prof. Muir's further results. In the first place there was evidence that for every dose of immune body attached to a red blood-corpuscle capable of taking up more than the simple M.H.D. (minimum hæmolytic dose), a dose of complement can be attached to the cellular protoplasm. This at any rate is true for small multiples of the M.H.D. of immune body. This fact of a definite quantitative relationship between immune body and complement taken with similar relationships found by Prof. Muir in practically all the very

complicated reactions he has examined, makes him inclined to doubt Bordet's idea of a mere sensitisation of red corpuscles by immune body. A further fact was observed, viz. that when corpuscles saturated with immune body are likewise saturated with complement, neither complement nor a combination of immune body and complement can be dissociated from the combination, but this very significant point has been brought out, namely, that immune body can be dissociated. This is an extraordinary circumstance, and raises the most difficult question, whether the immune body is really a link between the sensitive cell and complement. The question is now all the more difficult in consequence of the work of Bordet already described, in which that observer shews that an anti-immune body can exist which is operative against the complementophil group of the immune body,—this being the most definite evidence yet adduced that an immune body is in reality a link between a cell and a complement. Further consideration and investigation is necessary before a definite opinion can be expressed.

Again, Prof. Muir has adduced evidence in support of the view, that affinities capable of fixing complement are widespread in the body, and that even stromata of blood-corpuscles possess this capacity. That in the latter case a true fixation here occurs is indicated by these facts:—(1) That the complement cannot be detached by sensitised red blood-cells capable in other circumstances of taking up free complement; (2) that the complemented stromata, when heated to a temperature which destroys this cytolytic capacity of complement, no longer shew any capacity for taking up more complement; (3) that no combination of stromata and complement takes place at 0° C. If this occurrence of direct fixation of complement by cells be granted, then we might consider that immune body may not be a link between the cell and complement, but may cause a rearrangement of the atomic constitution of the susceptible molecules, so as to make complement more easily taken up. That probably some intra-molecular management does occur in hæmolysis is indicated by another of Muir and Browning's results. It was found that while complementoid could not prevent hæmolysis of sensitised corpuscles by complement, it could combine with the molecular combinations of protoplasm and immune body, which occur in the hæmolysed fluid when the dissolved corpuscles had been previously saturated with immune body. The special point here, however, lay in this, that the taking up of complementoid by the protoplasm + immune body combination could prevent this combination taking up complement which otherwise it could have done. This, in conjunction with the fact that though very little complementoid will enter into combination with sensitised corpuscles before lysis, a great deal will enter after lysis, shews that a molecular change, which is probably very complicated, occurs in the process.

We cannot enter further into the numerous questions of detail which these and other researches raise. We may say, however, that the tendency on the part of Ehrlich has been to account for complexity of action by supposing that in many instances a great number of closely

allied bodies are involved, and that the mechanism controlling the reactions of these substances is to be found in the inter-relations of ordinary chemical affinities; an important point in such a scheme is, of course, the presence of affinities of different degrees of avidity. That a multiplicity of reacting bodies exists may be said to have been established, but whether all the phenomena are to be accounted for on Ehrlich's scheme, may be considered doubtful. Facts which have emerged in the researches of both Bordet and of Prof. Muir raise the possibility that the apparent complexity of reaction is due to the influence of chemical processes of an order different from those present in reactions of an ordinary type. In fact, the close analogies existing between many of the reactions concerned in hæmolysis and the toxin-antitoxin reaction at once suggest the thought that probably the problems we have discussed with regard to the latter will arise here also. We have seen that questions of reversibility of reaction and of the possibility of phenomena of adsorption being present have arisen, and it is extremely likely that ultimately the processes of the neutralisation of toxin by antitoxin and those of hæmolysis will be found to be reactions of the same order. It will be noted that the complexity of materials, alleged by Ehrlich to be present in hæmolytic reaction, finds a parallel in the similar complexity which he asserted for the constitution of the soluble bacterial toxins. We have seen that the application of physico-chemical methods to the reaction of the latter has resulted in a position which is not altogether favourable to Ehrlich's original opinion. We feel that in the future these methods will be freely applied in the study of the problems of hæmolysis, and we must be prepared for modifications taking place in opinion regarding Ehrlich's original views as to the interactions of the substances concerned.

While Ehrlich's main fundamental observations have been accepted by all other workers, in respect to one class of substances described by him,—the anticomplements,—doubt has been cast on Ehrlich's views. Moreschi (243*a*) has shewn reason for believing that there is not the formation of a specific anticomplementary substance, but that the anticomplementary phenomena are due to complement being merely deviated from action with, say, an amboceptor. When the serum of one animal species is injected into an individual of another species, the serum of the latter may develop the capacity of forming precipitates with the serum of the former (*v.* p. 158, "Precipitins"). Thus, on injecting a serum containing complement (to obtain an anticomplementary serum), the conditions for such precipitin-formation are present. That the action is not specific was shewn in an experiment of Moreschi, in which the serum of a rabbit treated with egg-albumin could remove the rabbit complement capable of acting with rabbit immune body on ox corpuscles. Ehrlich's views on the action of anticomplementary serums must therefore probably be revised. It appeared to Pfeiffer and Moreschi (281) that the actions of anti-immune bodies were due to similar precipitin phenomena, but Browning and Sachs (19*a*) have adduced evidence that such anti-immune substances really do exist.

Ehrlich's View as to the Mechanism of the Formation of Immune Body.—It is important at this stage that we should consider Ehrlich's view of how the constituents of a hæmolytic serum come into being. First of all here we must again insist that the cytotoxic factor—the complement—is a normal constituent of an animal's serum, and that the immune body is the specific factor which the process of immunisation causes to appear in the serum. We emphasise this and at the same time again put forward one of the most important points to be kept in mind in our consideration of bacterial immunity, namely, that evidence has still to be sought for, there being during immunisation an increase of the amount of complement in the serum beyond the limits which may be found in the normal animal. We have thus here to do only with the question of the formation of immune body. Ehrlich's view follows the lines of his explanation of the formation of antitoxin. He considers that when such bodies as the red blood-corpuscles of an animal are placed in the body of an animal of another species certain unsaturated affinities in their protoplasm interfere by their presence, in a way which he has not explained, with the metabolism of the bodily cells. That such an upset of metabolism does occur is shewn by the fact that an animal may die after the intraperitoneal injection of even washed corpuscles from another animal. One factor in the metabolic upset caused by the foreign blood is that certain side-chains of certain body cells are saturated by side-chains derived from the corpuscles introduced. The cells containing them thus lose the services of affinities which are necessary to ordinary metabolism. As a result there is a production of new side-chains, and as immunisation progresses an over production similar to that occurring in antitoxin formation takes place, and finally there is the casting off of the side-chains into the serum, in which they form the immune body. In support of such a view von Dungern (92) brings forward certain facts. Thus, he believes that the side-chains of the red cells to which an immune body becomes attached are necessary, as the conception supposes, for the production of that immune body. He injected red blood-corpuscles saturated with inactivated immune serum, and found that in these circumstances no immune serum was produced. Here the active side-chains of the red cells were saturated and thus could not become attached to any affinities existing in the body of the animal into which they were injected. He further interprets the capacity of the cells of such organs as the liver, spleen, kidneys, lung, and brain to take up complement from a serum as evidence that there are in these cells affinities corresponding to the affinities of free immune body. These are the affinities belonging to the molecular complexes which when overproduced are cast off and actually become the immune body of the immune serum. The cells of bodily organs would thus be the source of the specific element in an immune serum. As to what cells are actually concerned in the formation of immune body Ehrlich gives no opinion.

The Hypotheses of Hæmolysis in relation to Bacterial Immunity.—We must now pass to consider the relationship of the researches on

hæmolytic action to the problems of immunity. We have stated that the essential facts of the hæmolytic action of a serum, namely, the necessity for the co-operation of two substances present in the serum, were first discovered in relation to the artificial intraperitoneal infection of animals with the cholera vibrio, and that similar facts have been adduced with regard to infections with typhoid. Neisser and Wechsberg (254) have demonstrated these fundamental facts in the cases of certain vibrios of the cholera group, and Shiga (311) has shewn for the dysentery bacillus, that inactivated goat-serum can be activated by fresh human serum. Bordet and Gengou (43) have made similar observations with regard to the serums of animals immunised against the organisms of plague, anthrax, and swine erysipelas, at least in so far that the immune body and complement are taken up. No lysis, however, occurred, and they have adduced no evidence that the bacteria were killed. There is thus no doubt that in immunisation against *many* bacteria (in our present state of knowledge the limitation is important) the capacity on the part of an animal for killing the bacteria is associated with the appearance in the serum of immune bodies, which render these bacteria susceptible to the action of the complement naturally present in the animal's body. In the meantime we simply take this as true in the form in which we have stated it. Whether in this form the statement represents the whole truth is a matter for later discussion. We may further say that we consider it to be unwise to generalise, as has been far too commonly done, from the particular cases examined to all cases in which bacteria are killed in the body. We may take it, however, that there is a general identity between the action of many antibacterial immune serums and the action of hæmolytic serums. The question now arises whether the death of the bacteria in an immune serum is dependent on a series of physical changes similar to those concerned in hæmolysis. We do not know what the essential feature of hæmolysis is, but evidently we must keep in mind the possibility that bacteriolysis is an essential phenomenon of bactericidal action. At any rate bacteriolysis may be of that kind of change which is inconsistent with the continued life of bacterial protoplasm. Research has disclosed the occurrence of actual bacteriolysis as an accompaniment of bactericidal action only in immunity against the typhoid and cholera groups of bacteria. On the other hand, since there is evidence in the cases of the bacillus of anthrax, the bacillus of swine erysipelas, the bacillus of dysentery, that substances of the nature of immune body and complement are concerned in a bactericidal action in which bacteriolysis cannot be said to be present, it follows that there is probably a community of essential process between bacteriolysis and certain types of bactericidal action. This, however, in no way justifies the assumption of necessary identity between bacteriolytic and bactericidal action which is very commonly made. In certain cases of immunity against bacteria it may be doubtful whether a bactericidal action ever exists in the serum. In support of this statement we may allude to the results obtained by Sir A. E. Wright and Dr. Windsor (377) working on the bactericidal

properties of human serums. Sir A. E. Wright (365) had previously laid the basis for measuring by a new method the bactericidal power of the serums, and, both alone (362) and also in collaboration with Dr. Windsor, applied this method to human serums, and obtained evidence that increased capacity for killing bacteria within the body is not necessarily correlated with increased bactericidal potency of the serum. In the cases of typhoid in man and the rabbit, and of cholera in the rabbit, it was shewn that after immunisation there was an increase of bactericidal power in the serum. On the other hand, in a case in which the treatment of a patient with dead cultures of *Staphylococcus pyogenes aureus* had resulted in an immunisation, as shewn by the disappearance of a tendency to furunculosis of some years' standing, there was no increase of bactericidal power in the serum. In ordinary unimmunised men there is usually present in the serum a considerable bactericidal capacity towards such bacteria as the *B. typhosus*. No such capacity existed with regard to the *Staphylococcus pyogenes aureus*, the micrococcus of Malta fever, the plague bacillus, and probably the *Streptococcus pyogenes* and the diphtheria bacilli. The absence of bactericidal effect towards the staphylococcus by animal serums had previously been observed by Dr. Nuttall (260). These researches open up a fresh field of inquiry, as they raise the question whether immunity against bacterial infection may not be due in different cases to different mechanisms.

Analogies between Hæmolysis and Bacteriolysis.—We may, however, say that apart from actual bacteriolysis the relation of the facts of hæmolysis are of importance from the standpoint of immunity against infective disease. This is the case not only because of the facility with which the processes can be studied and of the great exactitude of the methods which are applicable, but also because in the investigation of the relations of immune body and complement the molecular relationships of the substances through which protoplasm acts are again, as in the case of the toxin-antitoxin reaction, brought to view.

In the cases in which general resemblance has been established between the essential features of bacteriolysis and hæmolysis there are also striking resemblances in detail. Thus Pfeiffer and Friedberger (277) have adduced reason for believing that as with red blood-cells so with cholera vibrios, the protoplasm is capable of taking up many more amboceptors than are necessary for mere solution. If a lysing dose only of an anti-cholera serum be injected into a guinea-pig together with a M.L.D. of the vibrio, the lysis of the latter is followed by a development of an immune serum in the animal. On the other hand, if an excess of the immune serum is in the first instance administered no immune serum results. The interpretation given is that in the first case the lysis set free unsaturated bacterial receptors which stimulated amboceptor-production. In the second case, when lysis occurred the superfluous receptors being saturated with amboceptors could have no such action. Pfeiffer and Friedberger have further come to the conclusion that the receptors of the

cholera cells which can fix the amboceptors of an immunised rabbit are the same receptors which can fix the amboceptors of an immunised goat. Again, they (276) have shewn that against the latter an anti-immune body can be developed, and that it is effective against the cytophilic affinity of the amboceptor. Such facts indicate that not only in broad general principles, but also in the finer details, bacteriolytic action is analogous to the hæmolytic, and afford a justification for the labour expended in the investigation of the phenomena of the latter.

Bacteriolysis in relation to the Pathogenetic Effects of Bacteria.—In connexion with the relations, in certain cases, of bacteriolysis to the death of invading bacteria there arises a question which it will be well at once to consider. This relates to the effects which a bacteriolysis may have in the liberation in the body of the contents of the dissolved bacterial cells. The phenomena which here emerge constitute the basis of a very complex problem. In every artificial culture, and possibly when growing in the living animal body, whether an immune serum be present or not, bacteria are constantly dying, and their bodies are breaking up. In the case of fatal infections in the living body, Radziewsky has shewn that differences in staining reactions can be observed in the bacteria present in the tissues. These differences he, in all probability correctly, interprets as evidences that the cells are undergoing degenerative changes which end in death. Prof. Welch (354) also, in the case of the pneumococcus, has observed in exudations that bacteria situated both without and within cells shew alterations in staining reaction which certainly denote degeneration and death. We have seen that Bordet is of opinion that the hæmolysis which can be produced by exposing red cells to distilled water differs from the hæmolysis produced by an immune serum. We have thus to keep in mind the possibility that processes presenting similar differences occur in the bacteriolytic phenomena of infection. The mere recognition of this possibility, however, is not the most important consideration here. What we really have to think of is the effect of bacteriolysis, however it may have been produced. The most serious effect which can occur is the liberation of the intracellular toxins. It is only in the light of what occurs in immunity from infection that the action of these toxins can be properly understood. The relations of immune serums to the toxic substances present in bacterial cells have been studied by Pfeiffer and Wassermann (281) in cholera, by Pfeiffer and Kolle (278) in typhoid infection, and by Kolle (163) in the case of plague. In the case of cholera, amounts of a bactericidal serum, which were capable of killing the bacteria in from ten thousand to twenty thousand M.L.D. of living culture, were injected intraperitoneally along with in one case 3½ M.L.D. of living culture, and in another case 5 M.L.D. of the same; in two hours serious symptoms of intoxication set in and both animals died, the one in nine hours, the other in ten hours. That the bactericidal power of the serum had not failed was shewn by the fact that in one case no living bacteria were found in the peritoneal cavity after death, and in the other only a very few. Similar results were obtained

with typhoid serums; a thousand times the amount of serum capable of protecting a guinea-pig against infection with 1 M.L.D. of living bacilli could not protect an animal against about $2\frac{1}{2}$ M.L.D. of a dead culture. In the case of plague, Kolle, from old cultures from which the actual bacterial bodies had been separated either by filtration or centrifugalisation, obtained a fluid which manifested toxic properties. Repeated doses of this fluid were injected into horses with a view of immunising them. It was found, however, that their serum possessed no capacity of protecting animals against the dissolved intracellular poisons used in the attempt at immunisation. In connexion with this subject it may be noted that in one experiment Pfeiffer observed that the animals injected with the dead bodies of cholera vibrios and immune serum died in a shorter time than the control animals which received the dead bodies of the bacteria alone. These experiments furnish evidence that the immune serums of the bacteria concerned do not possess antitoxic properties towards the intracellular toxins to which such a great part of the pathogenetic action of the bacteria appears to be due. In fact the last-quoted observation of Pfeiffer makes it conceivable that the bacteriolytic action of an immune serum may actually increase pathogenetic effects, in that the solution of the bacterial protoplasm may hasten the passage of the intracellular toxins into the circulation. It thus appears possible, and even probable, that the intracellular toxins have no relation to the development of a bactericidal action in immunity against infection, and in this there is a striking contrast to what happens in the case of the extracellular soluble poisons. And, further, these toxins may play very little, if any, part in stimulating the animal body to resist a natural attack of an infectious disease. This helps us to understand what really takes place in the cases of fulminating intoxication as it occurs in some infections, such as some cases of scarlet fever, and some septicæmias, where death may occur in a few hours after the commencement of the illness. In such a case a rapid multiplication of the causal organism, followed by the death of a great many individual bacterial cells, causes a liberation of intracellular toxins, against the action of which the body has no protective mechanism. But, it is natural to ask, by what means does the body of an immunised animal gain the capacity of producing a bactericidal serum? We must consider the possibility that parts of the bacterial protoplasm which are in themselves non-toxic, but which are essential to the continued life of the cell, are the agents by which the bactericidal action originates—a conception which is quite intelligible on Ehrlich's hypothesis. The molecules of the intracellular toxins may have no affinities for cells in the animal body, and though they may act after the manner of the alkaloidal poisons, they may have little or no capacity for producing antitoxins. Other molecular complexes in the bacterial cell, and those on whose integrity the continued life of the cell depends, may have affinities for side-chains which are necessary to the vital metabolism of the animal body. Thus the production of anti-bodies—in this case immune bodies—may be stimulated, and bacteriolysis or bactericidal action results. But so far as an animal

fighting against a bacterial infection is concerned, its chance of survival may depend on whether by immune body, either naturally produced or artificially supplied to it and sufficiently complemented, it shall have killed all the bacteria produced by natural bacterial multiplication before the sum total of intracellular toxin present in its body has reached a minimal lethal dose. The acceptance of such a conception is, we must admit, not without its difficulties. These difficulties chiefly arise from the consideration of what occurs during immunisation. We have seen that one of the obstacles to the easy immunisation of animals against certain infections is that while immune body is readily produced, the natural amount of complement is probably not at all increased. But there may be a second obstacle to immunisation, namely, that there is set free at each fresh injection of bacteria (whether living or dead) an amount of intracellular toxin against which the body has no protection. It cannot be said that here we have experimental data sufficient to warrant the expression of an opinion on the questions involved. For in many cases during immunisation such large amounts of bacterial protoplasm as compared with the minimal lethal dose are employed that we must hesitate to say that no protection against intracellular toxins exists, or at any rate that the establishment of a tolerance similar to what occurs, say, in the case of morphine is not possible. But we cannot exclude the possibility that in certain cases antitoxic substances may not be developed against intracellular toxins. For instance, Metchnikoff, Roux, and Taurelli-Salimbeni (239), by the injections of toxic filtrates of cholera cultures, produced a serum capable of protecting an animal against this toxin which no doubt, as in Kolle's filtrates of plague cultures, contained intracellular toxins. These observers also found that the serum probably owed its effect to properties quite different from those possessed by a bactericidal serum produced by injecting the bodies of the cholera vibrio. A certain degree of antitoxin production is also stated by Markl (211) to have been observed by him by the injection of filtered plague-cultures. Such antitoxin-production is, however, as we have seen, denied by Kolle (163). In the case of the typhoid bacillus, Dr. A. MacFadyen (194) has, by employing the expressed juices of the organism, produced a serum protective against the living bacilli; he attributes its action to the endotoxins present in the fluid used for immunisation. So far as our present knowledge goes, we must admit the possibility that endotoxins can give rise to antitoxin formation. Such antitoxins are, however, probably formed by an animal with very great difficulty and in relatively small amount. The whole subject is at present beset with difficulty.

Points relating to the Therapeutic Use of Antibacterial Serums.—We have seen the analogies which exist between the bodies concerned in certain bacterial immunisations and those concerned in hæmolysis. It is natural that we should, as in the case of antitoxin development, inquire here also, on the one hand, as to the part played in recovery from disease by the development of substances in the serum, and on the other as to the

application of immune serums in therapeutics. The consideration of the former question is bound up with one to be presently considered, namely, the manifestations of cellular activity which occur in disease; we shall here confine our attention to certain scientific points in the therapeutical application of immune serums.

Lack of Complement.—The first point here is a corollary to the difficulty which arises from the fact that no increase in complement occurs during antibacterial immunisation. It follows from this that a fresh animal can by the injection of an immune serum only be protected against that number of living bacteria which can be killed by the combined action of the amount of complement it naturally contains plus the amount of immune body with which that complement can combine. If we leave the possible action of intracellular toxins out of account, and consider only the continued existence of the bacteria as the source of danger to an animal's life, the amount of complement in the body is the sole factor determining the number of bacteria which can be killed. Be there ever so much immune body introduced into an animal during an infection, even though that immune body become attached to bacteria in the tissues, the vitality of the bacteria will be unaffected unless sufficient complement be present to act on them through the immune body which they have absorbed. Wassermann (364) has shewn, in the attempted protection of guinea-pigs against typhoid infection by the injection of an antityphoid serum, that an animal may die even though it has so much free immune body present in its serum that when that serum is injected, together with typhoid bacilli into another animal, the second animal may in this way be protected against a fatal illness. The explanation is that the complement available in the first animal had been all used up before the typhoid bacilli were killed; the immune body present in its serum, however, when introduced into the second animal was complemented by that animal's serum; the second animal was thus in a position to utilise material which in the body of the first animal was practically inert matter. In this connexion it is important to note that some evidence has been adduced to shew that during infection the ordinary complement-producing function of bodily cells is interfered with. Schütze and Scheller (308) had investigated the effects of introducing washed goat-corpuscles intravenously into normal rabbits —the serum of the latter animal having *in vitro* a natural hæmolytic action on the erythrocytes of the former. If within a quarter of an hour the rabbits were bled, a marked fall in the hæmolytic capacity of the separated serum was manifest. This was shewn to be due to lack of complement, but in a few hours the blood regained its ordinary hæmolytic power. In an animal, however, in which an infection with the organism of hog-cholera had been practised, the recovery of complement after the injection of goats' corpuscles did not take place. This observation may be compared with that of Ehrlich and Morgenroth (109, p. 96), that in animals poisoned with phosphorus a disappearance of hæmolytic complement could be observed. These observations are of the highest importance if taken in conjunction with the fact already recorded, that even in immunisation

there is not any great increase of complement in the serum. The using up of this body in actual infection is thus very serious. In these circumstances it is natural that the artificial supply of the substance should be thought of. In certain cases this can be done, but the successful substitution of a foreign complement for that made by the infected animal is subject to many limitations.

The Neisser-Wechsberg Phenomenon.—In this connexion it has been found that in cases in which it is possible to supply complement to the infected animal it may not be safe to supply such complement except in certain doses. This results from the work of Neisser and Wechsberg (254), with which we shall now deal. These observers studied the effects of the action on the *vibrio Metchnikovi* of an immune body derived from the immunisation of rabbits with that bacterium, the complement used being derived from fresh rabbit-serum. They found that the immune body and complement, when brought in contact in certain quantity with a given amount of vibrio culture, manifested a definite bactericidal action, which resulted in the death of all the bacteria present; if, however, in similar mixtures there was placed a greater amount of immune body, the amount of culture and complement being kept the same as before, the bactericidal action was no longer manifested and the bacteria did not appear to suffer. They observed the same phenomenon in similar experiments with the typhoid bacillus and with the Nordhafen vibrio (one of the cholera group). In the latter case the phenomenon was obtained with four different complementary serums. Shiga (311) observed the same phenomenon in studying the bactericidal capacity towards the dysentery bacillus of immune body from the horse complemented with fresh horse-serum, and similar results have been obtained with the *vibrio Metchnikovi* by Lipstein (184). Neisser and Wechsberg's explanation of the occurrence is as follows:—As will be remembered, Ehrlich shewed for hæmolytic serums that the immune body apparently possesses a greater affinity for the susceptible cells than it does for complement, in that it will combine with the cells at 0° C., at which temperature it remains free from any combination with complement. Neisser and Wechsberg hold that similar affinity phenomena do not occur in the case of the relations of *bacteria*, immune body and complement. A case is supposed where in such a mixture there was excess of complement, that is, more than sufficient complement for all the immune body capable of being taken up by the bacteria. If, as with hæmolytic serums, the affinity of immune body for bacteria were greater than its affinity for complement, then if with excess of complement there was also excess of immune body the bactericidal effect would be the same. The bacterial side-chains would be saturated with immune body; the weaker complement would ultimately attach itself to the immune body and work its bactericidal action. If, however, the affinity of immune body for complement were greater than its affinity for the bacterial protoplasm, the occurrence of excess of immune body would have a different effect. The immune body would become linked to free complement and pass the

bacteria by; many side-chains of the bacterial cells might thus be unsaturated, and the bacteria might escape from the action of the complement and continue to live. This is an extremely hypothetical explanation of the phenomenon, and rests on the assumption that the immune body acts as a link between the susceptible cell and the complement—a possibility regarding which, as will have been seen, we prefer to keep an open mind. The question might be asked why a small amount of the powerful combination of immune body plus complement is more likely to attach itself to the weak affinity in the bacterial protoplasm than a large amount of the same combination? We prefer to accept no explanation of the Neisser-Wechsberg phenomenon, but merely to note that in the case of certain immune serums an excess of immune body appears when complemented to produce less bactericidal effect than a lesser amount of the same body. It may be stated that Gay (133*a*) has suggested an explanation of the facts similar to that given by Moreschi for the anti-complementary reaction.

Complexity of Antibacterial Serums.—We now pass to consider what constitutes the most serious limitation to the artificial supply of complement to an infected animal. This results from the probability that, as we have seen, immune serums are of a very complicated constitution, so that even in a single serum there may be several immune bodies and several complements acting. An illustration of how the views regarding this complexity are applicable to bactericidal serums may be gathered from the work of Wechsberg (349). This observer found that pigeons could not be protected against the effects of inoculation with the *vibrio Metchnikovi* by injecting inactivated immune serum from the rabbit. The reason was that there was no complement in the pigeon to make this immune body available. This was deduced from the observation that while inactivated rabbit immune serum could be activated by normal rabbit complement, pigeon serum neither had any natural bactericidal action nor could it activate inactivated rabbit serum. The pigeon could, however, be protected from fatal infection by administering inactive rabbit serum along with normal rabbit complement. If the pigeon were itself immunised against the vibrio, then it yielded a serum which was protective *in vivo* and also bactericidal *in vitro*. Even this serum, however, could not complement inactive rabbit serum, from which Wechsberg deduces that the complementophil group of the pigeon immune body was not identical with the corresponding group of the rabbit immune body. A curious observation was that if very large doses of the rabbit immune body were injected into the pigeon the animal did not die. Wechsberg's interpretation of this is that there may have been two immune bodies in the rabbit's serum, one of which—present in large quantity—did not find a sufficient complement in the pigeon's body; the other—present in very small amount—finding, however, an adequate complement. This example illustrates very well the exceedingly difficult problems which have to be faced in attempting to utilise for therapeutic purposes the knowledge acquired regarding bactericidal serums. With regard to the artificial supply of complement, it will be

recognised that no principle can be laid down which might form a guide in selection, and that at present the search can be only a process of groping in the dark, in which the trial in any given case of all the available serums in all possible combinations is the only hopeful measure. It has been suggested that, for any particular animal species, complements might be found in the serums of allied animals, but as yet this suggestion has produced little result. Ehrlich and Morgenroth have also suggested that in order to provide serums containing a number of immune bodies, some one of which might be capable of being complemented by an infected animal's serum, a mixture of serums from several different species, all immunised against the infected agent, might be useful. Such serums might be included among the polyvalent serums, of which we shall speak later.

There are yet other limitations to the artificial supply of complement to which allusion must be made. In the first place, immune serums rapidly lose their complements on standing, so that in a few days there is very little of this substance left. In the second place, we have seen that when foreign complement is injected into an animal its serum manifests anti-complementary properties. If (as, however, there is reason for doubting) such anti-complement is of the same nature as the other anti-bodies, its formation will, according to Ehrlich, proceed along the usual lines resulting in the casting off of superfluous side-chains into the plasma. The development of these anti-complementary properties may result in the neutralisation of any foreign complement still remaining or subsequently introduced. Even if such a process do not occur, the fixation of complement in bodily cells may, it is evident, prevent foreign complement being utilised for the purpose for which it was introduced into the infected animal. It has actually been shewn by v. Dungern (92) and others that bodily cells can take up complement, so that these remarks have not merely a theoretical interest, and the difficulty of the situation is thereby increased.

Some attempts have been made to stimulate the production of complement in the body. Issaeff (148) had early in the investigation of artificial immunity adduced evidence to shew that the resistance of animals to cholera could be slightly raised by the injection of salt solution, albumin, urine, nuclein, etc., and Dr. Bulloch (57) and others have shewn that complement can be increased by the injection of a vegetable casein (aleurone). Such attempts are well worthy of further attention.

Our general conclusion here must be that in the case where immune body is introduced in order to assist an animal in its fight against bacterial invasion, such immune body is best made available when the animal itself can supply an adequate complement. At present the problem of the artificial supply of complement cannot be said to have been solved. It is not surprising, therefore, that the knowledge gained regarding bactericidal action still awaits its practical application in disease.

The Constitution of Normal Bactericidal Serums.—Just as in normal

serums hæmolytic elements occur, so many of these serums normally possess bactericidal properties. As we shall see presently, the substances responsible for such properties were called by Buchner *alexins*. A very striking property of these substances, which was first observed by Dr. Nuttall (*v.* p. 129), was their thermolability. In all probability this bactericidal action falls into line with the facts known regarding hæmolytic serums and immune bactericidal serums. In speaking of naturally hæmolytic serums, we have seen that the hæmolytic property is here also lost on the application of heat at a temperature such as destroys bactericidal alexins. We have also seen evidence for believing that natural hæmolytic action is due to the presence of a thermostable *zwischenkörper*, in virtue of which the thermolabile alexin or complement acts. It is natural that we should ask whether similar facts hold good of the normally bactericidal serums. There is little doubt that thermostable substances concerned in bactericidal action do occur. Thus Wechsberg (349) found evidence that the addition of heated normal rabbit-serum increased the bactericidal action of guinea-pig blood towards typhoid bacilli. Malvoz (203) has adduced experiments to shew that the normal serum of the dog contains a thermostable substance, which along with the thermolabile serums of the rabbit, the rat, and the guinea-pig is taken up by anthrax bacilli. This has been confirmed for rabbit blood by Bail (12) by bactericidal experiments. These results suggest that *zwischenkörper*, analogous to natural hæmolytic *zwischenkörper*, do occur. So far as we are aware, no attempts have been made to obtain a bactericidal serum free from the thermostable body, in such a manner as has been done with hæmolytic serums when the *zwischenkörper* have been removed by keeping sensitive cells in contact with the active serum at 0° C. It is highly likely, however, although the subject requires further investigation, that the bactericidal properties of serums are due to the presence of thermostable and thermolabile bodies analogous to the substances concerned in hæmolytic action. It is probable that light would be thrown on the numerous apparently contradictory properties of bactericidal serums by further investigation of these constituents, and it is here that the minute researches which have been pursued regarding the constituents and interactions of hæmolytic serums may be useful. Thus, Wassermann (343) observed that in the typhoid infection of the guinea-pig the beneficial effects of goat immune serum were limited by the deficiency of complement. This deficiency could be overcome by the injection of normal ox-serum.

While Ehrlich has expanded his side-chain hypothesis of toxin-formation to cover the case of the development of immune body, and while there is some evidence in support of his view, it is evident that we are here dealing with a much more complex phenomenon. We have not, as in immunisation against a soluble toxin, to do with a fluid which may find its way to any part of the body and pass freely into the bodily cells. We have to deal with solid bodies, be they bacterial or animal cells, and it is the union of side-chains in these foreign cells with side-chains in the cells of the animal being immunised to which we have to look for the production

of immune body. Two possibilities to explain how this comes about might be advanced. In the first place, it might be necessary for the foreign cells to be taken up by the body-cells in order that the necessary molecular union might occur; or, secondly, the side-chains of the foreign protoplasm might be dissolved out into the fluids of the host, and thus act as if they were soluble toxins, though of course they need not be themselves toxic. A third possibility, suggested by the results of Muir and of Morgenroth, might be considered. It is possible that the mere contact of the foreign cells introduced with the cells of the body might result in a transference of molecules from the one to the other. We shall presently consider the taking up of foreign cells by bodily cells, and the possible part played by such an ingestion in relation to immunisation; but we may say here that apart from the facts brought forward by von Dungern as to the impossibility of obtaining an immune serum by means of cells saturated with immune body, we are still in want of evidence bearing on the mechanism of the genesis of immune bodies, and we have no conception of how the serum comes to possess complementary bodies.

The Phenomenon of Phagocytosis

In discussing the previous theses we have recognised two of the striking facts regarding the development of immunity against bacterial disease, namely, the appearance in the serum of immune animals of antitoxic substances and of bactericidal substances. We have looked on the occurrences simply as facts regarding serums. We have only looked partially at evidence for the origin of the special substances occurring in the serum, and we have not inquired how far the properties of the serum represent the properties of the plasma of the circulatory blood. There are thus many questions regarding immunity still open. The chief of these will emerge in the discussion of our third thesis, which is as follows: *When bacteria gain an entrance to the body they are frequently taken up in a living condition by cells and there is evidence that they are there destroyed; such an occurrence is denominated phagocytosis. There is very strong evidence that in an animal recovering from disease, and in an immune animal, the capacities of phagocytic cells are especially great.*

We are now brought in contact with the hypothesis associated with the name of Metchnikoff. This hypothesis in its earliest form, and even in its more recent developments, covered the whole field of immunity. In its original form its author (236) looked on the taking up of the invading bacteria by the leucocytes of the blood, and by cells derived especially from various endothelia, as the essence both of recovery from disease and of artificial immunity. This view was conceived before the true pathology of bacterial action, especially where that action depends on the elaboration of toxins, was understood, and before the antitoxic and bactericidal properties of the serums of immune animals had been recognised. As investigation revealed new aspects of the infective

processes, Metchnikoff (237) recognised the necessity for modifying and elaborating the hypothesis to suit the progress of knowledge, with the result that a very barren controversy has raged between its upholders, who would strain the phagocytic capacity of cells to meet every phenomenon of immunisation, and its opponents, who, without being able to substitute the activity of any other group of cells in immunisation for that of the phagocytes, have yet denied to these cells the function assigned them by Metchnikoff, or at any rate have without reason ignored the possibility of their exercising such functions; in the following remarks we must attempt to hold an even balance between the opposing schools. The chief modification which has taken place in Metchnikoff's opinion is that he recognises the complexity of the processes at work, especially in bactericidal action, and inclines to the view that, while actual phagocytosis is necessary for bactericidal action in some of its phenomena, other phenomena are to be explained by phagocytic cells producing, in the serum, substances necessary for the death of bacteria. We shall go into this matter in detail later.

Metchnikoff's views on the part played by phagocytosis in the local reaction, which may occur in a bacterial invasion, and whose phenomena are of the nature of an inflammation, have been gone into at length in the article on that subject (*see* "Inflammation," vol i. p. 741). The actual cells which in the body may be attracted to bacteria, and which may perform phagocytic functions, have there been fully described. We will therefore confine our remarks to the statement that the phagocytes are divided by Metchnikoff into two groups, the *microphages* and the *macrophages*. Of the microphages the chief example is found in the polymorphonuclear leucocytes of the blood. As types of the macrophages we may take the large mononuclear hyaline cells of the blood and the granular mononuclear cells common in serous exudations, the varieties of which have been described by different authors under various names. The relations of these cells to each other, to the hyaline cells of the blood, and to certain cells occurring in the splenic pulp cannot be said to be as yet made clear. Further, it is not known what relationship, if any, they bear to the cells lining the lymph-sinuses of lymphatic glands and the sinuses of the splenic pulp. To these cells, under the name of fixed phagocytes, Metchnikoff attributes functions allied to those of cells which move freely in blood-vessels or lymph-spaces. To understand the relationships of phagocytosis to immunity, we must clearly recognise the relations of the processes included under the term inflammation to bacterial infection generally. In speaking of the pathological effects of bacterial action, we pointed out that these are to be classified as partly the expression of injury to the tissues, and partly as the expression of a vital reaction of the tissues against the bacterial invasion. Any particular case of inflammation is a complex of such phenomena manifested in a particular locality in the body. But the process called inflammation is only a particular example of what follows bacterial invasion. There may be injury with hardly any reaction, as in many rapidly

fatal cases of infection; there may be reaction with only a small amount of injury, as happens in immunisation procedures. The prominent feature of inflammations and of reactions without much injury is the activity of the group of bodily cells termed phagocytes by Metchnikoff, but which we should prefer to call the reactive cells—thus avoiding undue emphasis on one of their functions. Whether or not the degenerative changes characterising what is called inflammation occur in any case, we now proceed to study the cellular reaction in its general relationships as being a phenomenon of very great frequency when the body suffers a bacterial invasion. In a local inflammatory reaction the result of the efforts of reactive cells may be, and very often is, the death of the invading bacteria. The occurrence of local inflammation is often an incident in the process of immunisation, especially in antibacterial immunisation, such as immunisation against the *Streptococcus pyogenes*; in these inflammations actual phagocytosis, or the taking up of bacteria by cells, is a frequent occurrence. In the resultant immunisation, however, there is some change wrought in the body generally. Every phagocyte in the body and every drop of the animal's serum may become possessed of new properties. The injection into any part of the body of, say, one M.L.D. of the bacteria against which the animal is immune may now be followed by none of the former inconveniences. It is the source of this *generalisation of effect* that we have to think of in considering the relationship of phagocytosis to immunity.

In studying the problems of immunity from the standpoint of the phagocytic hypothesis we shall find that a consideration of the phenomena of recovery from disease plays a large part. When an animal is the subject of infection by living bacteria and recovers, by what means has the death of the bacteria been brought about? According to Metchnikoff's view, it is entirely in virtue of the phagocytic capacities of certain cells. The bacteria are taken up into the cellular protoplasm and are there killed. If a sublethal dose of bacteria be administered the phagocytes soon take up all the organisms; if a lethal dose be present then either the phagocytic reaction is insufficient or the phagocytes are absolutely repelled. There can be no doubt that phagocytosis is a very common occurrence, and also that the movement of amœboid cells towards bacteria and the gradual incorporation of the latter can be observed microscopically. The questions which have been raised are, whether phagocytosis is or is not universal in recovery from infection, and whether an extracellular destruction of bacteria does not also take place.

The Taking up of Living Bacteria by Phagocytes.—With regard to the first question there arises another, namely, as to whether, supposing that in all bacterial infections phagocytosis does occur, the bacteria present are all taken up into cellular protoplasm. With regard to the first of these questions, there is little doubt that in bacterial infections phagocytosis is practically universal. It can be observed with the septicæmic streptococci and staphylococci, with the pneumococcus,

the gonococcus, the *Micrococcus melitensis*, the *Bacillus anthracis*, the tubercle bacillus, the leprosy bacillus, the *Bacillus pestis*, in fact in all the bacteria associated with ordinary human infections. Further, though the question has not been investigated in all cases of phagocytosis, evidence has been found, in cases where it has been sought for, that the organisms are taken up in a living condition. Thus Metchnikoff (237, p. 151) observed in an infection of the frog with a motile organism like the *B. pyocyaneus* that when the bacteria were taken up by the leucocytes they could be seen for a time executing active movements within the cellular vacuoles in which they were contained. Further, if such cells which had *recently* taken up bacteria were removed from the animal's body and kept at a temperature at which they would die, active proliferation of the bacteria took place. Again, Metchnikoff (227) has pointed out that living bacteria do not stain with an old aqueous solution of vesuvin (bismarck-brown) while dead bacteria are stained. Now in cells containing bacteria some of the latter do not stain, while the greater number do. The fate of the bacilli when they have been taken up is, according to Metchnikoff, that they are killed and digested. The death of the bacteria may be delayed for a considerable time. Thus, Mesnil (224) found evidence that living and virulent bacteria were present in the cells of the frog's lymph-sac several days after injection, and further that the virulence of the bacilli did not appear to have been affected by their sojourn in the phagocytic cells. The bacteria on being taken up by the cells are frequently observed to be lodged in vacuoles in the cellular protoplasm. That the fluid contents of these vacuoles manifest an acid reaction when the cell is treated with a 1 per cent solution of neutral red, is taken as evidence that they contain a free acid, and thus resemble the contents of the digestive vacuoles of many protozoa. The further fact that whereas the stain named has no colouring effect on living bacteria, but gives the acid tint to bacteria taken up into phagocytes, indicates, according to Metchnikoff (237, pp. 89, 192), that the bacteria are imbibing the acid, and are probably being prepared for the digestive action of the intracellular ferments or cytases, of which we must speak more in detail later.

Phagocytosis in relation to Recovery.—Metchnikoff's view of the course of events which occurs in recovery from disease may best be illustrated from his work on the inoculation of pigeons with the bacillus of anthrax (229). The pigeon shews considerable resistance to this organism, so that if a series of individuals be inoculated with an ordinary culture only about half die. Opportunity is thus afforded of comparing the course of a fatal with that of a non-fatal illness. Within four hours of the subcutaneous injection of the bacilli local inflammatory appearances with leucocytes occur, and the taking up of the bacteria by both the *microphages* and *macrophages*. When a non-fatal event is to occur it is observed, in from twenty-four to forty-eight hours, that very few bacilli remain free; while in cases which will

end in death the number of bacilli incorporated is markedly less—the majority being free. The bacilli within the phagocytes, whilst maintaining their form, shew signs of degeneration, such as are indicated by alterations in the appearance of the protoplasm and in staining reaction. Where much phagocytosis has occurred the free bacilli may shew similar degenerative appearances, which are attributed to the liberation of the organisms either in the living body or in the course of the microscopic technique by the breaking up of the cellular protoplasm. Some of the apparently normal bacilli present in the exudations of animals destined to recover may be looked upon as having died from causes similar to those which account for the death of many individuals in any ordinary artificial culture. In any case the criterion by which the probable issue is to be judged is, whether the majority of the bacilli is or is not incorporated by phagocytes. When the phagocytes take up the effective majority of the microbes the latter gradually die and are digested, the irritative local phenomena subside, and the animal returns to the normal. With regard to the active phagocytes, many may return to the blood-stream through the lymph, but in the case of many of the *microphages* they are often in turn taken up by *macrophages* and terminate their existence in a manner analogous to what occurs in the case of many effete leucocytes in the spleens of normal animals. In a non-fatal illness the bacteria are almost, if not entirely, confined to the point of inoculation. When a fatal illness, on the other hand, is imminent a more general distribution of the bacilli is observed, but, according to Metchnikoff, phagocytic activity in different parts of the body may still be manifested. Thus, he observed, in the anthrax of pigeons, bacilli taken up in the liver by Kupffer's cells, by the endothelium of the hepatic vessels, and by the cells of the splenic pulp. In generalised infections the occurrence of free bacteria is a marked feature. This outline of what may be seen in anthrax in the pigeon may be taken as Metchnikoff's views as to what occurs in fatal and non-fatal infections, and of the part he assigns to the phagocytic activity of cells in infective processes.

Phagocytosis in relation to Immunity.—If we turn to what occurs in the infection of animals artificially immunised, we find that here also Metchnikoff considers that the main factor is the activity of the leucocytes. Thus, he compares the course of events in an infection of the anterior chamber of the eye with the *vibrio Metchnikovi* in an immunised guinea-pig with what occurs in an ordinary animal. In both there is at first a general ophthalmic inflammation with opacity of the cornea. At the end of four hours in the unimmunised animal the fluid in the anterior chamber contains many vibrios and almost no leucocytes. Active multiplication of bacteria goes on, the body generally is invaded, and death results. In the immunised animal, on the other hand, many leucocytes are present which already contain bacteria in their protoplasm. This phagocytosis goes on, and though there is evidence that the bacteria are taken up in a living condition they ultimately perish.

Metchnikoff's work on phagocytosis led him to formulate a hypo-

thesis to explain all the phenomena of recovery from disease and of immunity. This was to the effect that when bacteria gained an entrance into the body the phagocytic cells were either attracted towards them or repelled. If phagocytes were attracted in sufficient numbers, and after incorporating the bacteria killed them, recovery of the infected animal took place. If, on the other hand, the phagocytes were insufficient, the bacteria multiplied, and the animal died. The termination of an infection in nearly all cases would often depend on the number of bacteria introduced; a non-lethal dose would be disposed of by phagocytes. As a consequence of such a successful combat, the bodily cells might acquire a greater capacity for killing the bacteria in question, and thus an immunity might be set up. Immunity against bacterial infection is solely a question of an increase in the phagocytic activity of the bodily cells.

The hypothesis has given rise to enormous controversy. This has mainly arisen from the facts regarding the occurrence of bactericidal actions in serums, which came into prominence soon after Metchnikoff's earliest publications, and the discussions have mainly turned on whether the destruction of bacteria in the animal body takes place within or without the bodily cells. It has thus been common to contrast humoral with cellular conceptions of immunity, though the demarcation is not justified by facts; and, further, those who have worked most at the subject would be least inclined to range themselves as adherents of any hypothesis.

Phagocytosis in relation to the Properties of Serums.—Amongst the early criticisms to which Metchnikoff's hypothesis was subjected, that of Dr. Nuttall (260) was most important. This observer, studying the effect of inoculation of the naturally immune frog with anthrax, observed that phagocytosis occurred in about 16 hours after inoculation, and continued up to 90 to 120 hours. He made a numerical estimation of the relative numbers of bacilli which during this phagocytosis were within and without the cells, and found that only from 50 to 70 per cent were taken up by the leucocytes. The extracellular leucocytes often shewed degenerative changes, and similar changes were visible in hanging-drop preparations of frog's lymph infected with anthrax bacilli. By keeping individual bacilli continuously under observation, he watched the development of these appearances in bacilli that had never been taken up into leucocytes. This last observation is of very great importance in view of Metchnikoff's opinion that the apparent extracellular degeneration was to be accounted for by the view that the affected bacteria had escaped by the breaking up of phagocytic cells. Dr. Nuttall subsequently noted that the exposure of bacilli to the serum in such circumstances, *i.e.* when the organisms were partly contained in cells and partly free, was followed by death; this was proved by the observation that no growth occurred when the bacteria were transferred to nutrient media. He also first observed that the bactericidal properties of such a serum were lost when it was heated to 52° C. for half an hour. Dr. Nuttall also noted similar bactericidal effects of serums on such organisms as the *B. subtilis* and the *B. megatherium*, which, so far as is known, do not usually manifest pathogenetic effects. These results were

followed by the investigations of Buchner (50), who, working along similar lines with several bacteria, but especially with the typhoid bacillus, noted the bactericidal properties of the serum and the loss of these properties when the serum was heated for half an hour to 55° C. It may here be parenthetically remarked that while the degree of temperature necessary for the destruction of bactericidal action varies in particular instances, Buchner's result may be taken as covering the majority of cases observed. Buchner called the bactericidal bodies *alexins.* On account of their susceptibility to heat, of their precipitation by ammonium sulphate, and of their sharing with such a ferment as invertin the curious property of being protected against the action of heat by the presence of ammonium sulphate, he placed them amongst the enzymes. There is no doubt that the thermolabile substances of Nuttall and the alexins of Buchner are the complements that we have already fully discussed. Nuttall and Buchner's work gave rise to many criticisms. For instance, Fischer (121) attributed the bactericidal actions of serums to plasmolysis caused by the transference of bacteria to a fluid different from that to which they had been growing,—a view which is probably negatived by the existence of specificity of bactericidal action in serums.

The main effect of the work of Nuttall, Buchner, and other investigators along similar lines, was to cause Metchnikoff's views on immunity to be questioned, and to confirm the tendency we have alluded to as already in existence, to substitute for a cellular a humoral conception of immunity. It thus became common to consider that recovery from infective disease in an ordinary animal and the insusceptibility of immunised animals might be due to the bactericidal qualities of their serum. On the possible sources of these bactericidal properties little attention was bestowed by the humoralists. A fierce controversy raged from about 1888 onwards between the upholders of the two views. Dr. Nuttall had observed that the serum of a sheep immunised against anthrax possessed greater bactericidal action than that of an untreated sheep, and Behring (18) attributed the high degree of resistance to anthrax possessed by white rats to bactericidal properties of their serum, which could be demonstrated *in vitro* towards the organism in question. Behring and Nissen (23) had observed that while the serum of ordinary guinea-pigs had no bactericidal effect on the *vibrio Metchnikovi,* the immunisation of such animals against the bacterium was accompanied by the appearance in the serum of bactericidal properties towards the vibrio. Metchnikoff himself (230) confirmed this observation.

As illustrating the progress of this controversy and the indirectness of the evidence often brought to bear on the questions at issue, we may refer to certain researches on the bactericidal qualities of the serum of the white rat. Dr. Hankin (144) had brought forward evidence that the serum of this animal when added to anthrax bacilli and introduced into the susceptible mouse prevented the development of anthrax; and Ogata and Jasuhara (264), working with frog and dog serums, adduced similar experiments. Metchnikoff and Roux (238) confirmed this obser-

vation, but pointed out (in accordance with Dr. Hankin's results, but contrary to what occurred in the analogous experiments of the Japanese observers) that if the serum and the bacilli were introduced at different parts of the body no preventive effect was produced. On further inquiry they compared the different appearances presented locally in a mouse infected with the mixture of serum and anthrax *spores* with those in a mouse inoculated with spores alone, and they found that the great difference noticeable was that in the former there was an accumulation of leucocytes which did not occur in the latter. These leucocytes took up nearly all the spores, which, however, began to multiply after a few days and killed the animal. From this the authors deduce that the serum has no effect in causing an immunity in the susceptible animal when numbers of vegetative bacilli and serum are injected without subsequent fatal result. All that happens is that the bacilli actually introduced with the serum are killed.

The general conclusion of the earlier controversy may be said to have been that normal serums did possess bactericidal properties, which probably depended on the presence of specific proteid substances. This bactericidal action was manifested towards both pathogenetic and non-pathogenetic bacteria. Its existence in relation to any particular bacterium could not be certainly correlated with any immunity possessed by the animal from which the serum was derived. Thus, as Metchnikoff (228) pointed out, the serum of the rabbit and of the dog had equal bactericidal properties towards the bacillus of anthrax, though the former animal was very susceptible and the latter practically immune to the disease. No deduction could thus be made as to the bearing of the possession of a bactericidal serum on the existence in an animal of natural immunity towards a disease. Nor, on the other hand, taking into account such observations as those of Dr. Nuttall on the occurrence of intracellular degeneration, could the actual taking up of bacteria by phagocytes be looked on as proved to be an absolutely essential factor in the mechanism of immunity. On the other hand, phagocytosis had to be recognised as a very constant concomitant of recovery from disease, as it occurred in cases of non-fatal illness both in unimmunised and in immunised individuals. In fact, the upholders of a purely humoral hypothesis have never brought forward any case of immunity against bacterial invasion in which phagocytosis is absent.

There is one general remark applicable to all experiments on bactericidal action, namely, that the results may depend very largely on the number of bacteria employed. A serum may be bactericidal, but in a given quantity may only be capable of killing a certain number of bacteria. If a greater number of bacteria be added, then no bactericidal action may be apparent. A very common technique for testing bactericidal action *in vitro* is to add a given quantity of the organism to an amount of serum, and after the expiry of the periods of observation to transfer small measured amounts of the mixture to melted tubes of media, which are then plated. The bactericidal action is estimated by counting

the colonies which develop on the plates after incubation. It is evident that if the period of contact between the serum and bacteria be at all protracted, and the organism be (as is frequently the case) a rapidly multiplying one, any initial destruction of bacteria may be counterbalanced by the subsequent multiplication of the remaining individuals. We shall see later that even in the living body there may be a using up of bactericidal material. Thus, the fluid of pus may be less bactericidal towards the causal bacteria than serum separated from the blood of the individual animal in which the abscess has been formed. If such an action is in reality pronounced, then it is difficult to see how bacteria are not killed more readily when introduced intravenously than when they are placed in a subcutaneous pocket, in which one would think the bactericidal substances would be quickly exhausted, and where facilities would be wanting for fresh supplies coming in contact with invading bacteria.

Pfeiffer's Phenomenon in relation to Phagocytosis.—The position just described may be taken as that arrived at in consequence of the earlier criticisms of the phagocytic hypothesis. We may now proceed to consider phagocytosis in the light of our present knowledge of the subject. It is round the significance of the Pfeiffer phenomenon that discussion here has chiefly turned. We have already described the features of this phenomenon and the factors involved in the bacteriolysis which occurs. According to Metchnikoff, however, the key to the situation lies in the recognition of the part played by phagocytes in the reaction, and of the fact that the properties of the serum depend on the escape of substances from phagocytic cells. He (231) stated that if a non-fatal dose of the cholera vibrio were injected into the peritoneal cavity of an ordinary guinea-pig the following sequence of events occurred. If the peritoneal fluid were examined within an hour or so after the injection the leucocytes normally present were found to be apparently less numerous than usual, the bacteria were free in the fluid, and did not manifest the appearances found when Pfeiffer's phenomenon was present. After this time leucocytic exudation with phagocytosis occurs, so that at the end of eight hours the fluid contains no free bacteria. The bacteria taken up manifest within the cellular protoplasm the granulation characteristic of the Pfeiffer phenomenon, although the fact that living cultures can be obtained from the peritoneum up to twenty-four hours after inoculation shews that it is some time before the actual destruction of the bacteria is completed. The important point here is the apparent diminution of the leucocytes immediately after the injection of the vibrios.

As we have already seen, two bodies are concerned in the Pfeiffer phenomenon—the thermostable immune body and the thermolabile complement. Although Metchnikoff's views on this matter are rather indefinitely expressed, we gather that he attaches significance to the resemblances between the intracellular appearance of vibrios taken up by phagocytes in an ordinary guinea-pig and the appearances manifest in the extracellular destruction occurring in the peritoneal fluid of an

immune animal. His view of the mechanism of the destruction of bacteria when once they have been taken up by phagocytes, is that they are acted on by certain intracellular ferments which he names *cytases*. Now granting, as Metchnikoff would do, the existence in the serum of an immune animal of thermolabile and thermostable elements concerned in bactericidal action, we have to inquire as to his views on the relation of these substances to the cytases concerned in the intracellular destruction and digestion of bacteria. His position here, in effect, is that, in composition in respect to bactericidal bodies, the serum does not correspond with the *liquor sanguinis* of the living animal. The evidence on which this is based is somewhat as follows. As we have seen, the serum of a guinea-pig immunised against cholera contains, like the peritoneal fluid, both immune body and complement. Bordet (33), however, states that the œdematous fluid produced as the result of causing passive congestion in the leg of an immune guinea-pig does not in the fresh condition give rise to the Pfeiffer phenomenon. It does do so, however, if some serum from a fresh guinea-pig be added, though it is not so potent as the immune serum. The fluid must thus contain immune body without complement. Bordet, on trying a similar experiment with fluid from the anterior chamber of the eye of an immune animal, found no evidence that either immune body or complement were present. The deduction from these experiments is that the poorer a body-fluid is in cells of the phagocytic type the less likely is it to manifest bacteriolytic properties. Again, Gengou (136) compared the properties of the plasma derived from uncoagulated blood with those of the serum obtained from clotted blood in the ordinary way. The method employed to prevent coagulation was to receive the blood into tubes coated internally with paraffin, and to precipitate the corpuscles by centrifugation. He found that when in such animals as the rat, the rabbit, or the dog, the serum manifested a definite bactericidal action, the plasma was either not at all bactericidal or only manifested a slight potency, associated perhaps with the slight degree of coagulation which, even with the precautions described, sometimes took place. The organisms used were those of anthrax, typhoid, cholera, and the *B. coli*. Gengou did not apply this method to the case of immune serums, but the results are accepted by Metchnikoff as proof that, in the normal fluids of the body, complement does not occur in a free condition. Falloise (119), however, has applied this method to certain hæmolytic serums, and found that plasma as well as serum contained complement. The whole subject requires further inquiry.

Accepting this view for the moment, we may inquire how the Pfeiffer phenomenon comes to be manifested in the peritoneal cavity of the immune animal. The key to this Metchnikoff finds in the phenomenon of the disappearance of cells from the peritoneal cavity when the bacteria are introduced. This he describes as due to what he terms *phagolysis*, though to what extent he holds that an actual solution of the phagocytic cells occurs is not quite clear. He states (237, p. 236) that these cells appear gathered in clumps in the great omentum, and a

it in the highest degree important that the local manifestations of cellular activity should be correlated to any properties which may simultaneously appear in the body-fluids. From what has been said of Metchnikoff's views, it is evident that this last point is the crux of the whole question. The only modification his earlier views have undergone in their latest presentation is in the matter of admitting that immune body may during life be set free from the cells producing it; but seeing he holds firmly to the opinion that complement never is found free in the body-fluids during life, it is manifest that it is only by actual phagocytosis that the death of bacteria can be accomplished, except in so far as the setting free of complement by phagolysis renders extracellular destruction possible. We have no data for determining to what extent phagolysis occurs and what part it may play in natural infections. It is evident that its occurrence is probably not limited to such events as the injection of normal saline solution or of bouillon. Nor is it essential that an actual solution of the cells concerned should be a necessary antecedent of their giving up to the surrounding fluids the substances through which they act. Whatever the normal functions of the leucocytes may be, it is certain that the ingestion and digestion of particulate objects is a comparatively rare occurrence with them. Thus, in ordinary circumstances the addition by leucocytes of substances to the circulating fluids of the body, in the same way that the cells in the body are constantly doing, is quite possible. The growth of bacteria in such a situation as the peritoneal cavity, and the elaboration by them of toxins, might constitute a cellular injury sufficient to cause substances usually intimately bound in cellular protoplasm to pass out into the surrounding fluids. It cannot, however, be said that we possess proof that such an excretion does actually take place.

Meanwhile stress must be laid on the complexity of the cellular activities manifested in such an event as the peritoneal reaction. We may draw an example from the very careful examination of the subject by Dr. Beattie (16), who, while having no doubt that the macrophage cells of the peritoneum can ingest living bacteria, cannot be certain that the microphage cells are capable of taking up any but dead organisms. Sometimes in infections there is evidence of the predominant activity at one stage of the process of one type of cell, at another of another type of cell. Thus Dembinski points out that in the infection of pigeons with the bacillus of avian tuberculosis there is first a slight phagocytosis by polymorphonuclear cells, while ultimately, and probably of greatest importance, there is a phagocytosis by the mononuclear macrophage cells. Reference may be made to one point in connexion with the complexity of the cellular manifestations observed in local infections. Whatever the significance of the presence of immune body and complement in serum may be, a very striking feature of an immune serum is, as we have seen, that while immune body is present in great amount there is no proportionate increase in complement. Metchnikoff appears to hold that the presence of these bodies in a serum is merely an indication that

the intracellular ferments present in phagocytes have passed out of the cells. It is evident, therefore, that during immunisation a change in the chemical activity of the cellular protoplasm has occurred. But as regards two important factors in the capacity possessed by the cells for dealing with invading organisms, there has been a lack of correlation, for while one substance has been increased the other has not. It must thus be left for future decision whether the two substances are formed in the same cell or whether there may not be a symbiosis between the numerous cells which take part in a reaction.

The Mechanism of Chemiotaxis.—We must now consider one or two further points regarding phagocytosis. We have seen that in cases in which Metchnikoff's view, that the mechanism of immunity consists essentially of a phagocytosis, may hold good, observations on phagolysis indicate that there is in the process a chemical activity on the part of cells in producing their intracellular ferments in unusual degree. The facts are not accounted for by a mere increase in the number of cells concerned in the process. But it is evident that intracellular activity is only one aspect of the processes of recovery and immunisation; the metabolic activity of the leucocytes must be secondary to their coming into actual relation with the bacteria which they are to take into their protoplasm. The article on "Inflammation" deals with the facts with regard to the occurrence of the attraction, manifested towards certain bacteria by phagocytes, which is known as positive chemiotaxis, and of the repulsion by—or, at any rate, the indifference towards—the bacteria exhibited on other occasions. A striking example of such a phenomenon is furnished by an observation of Bordet. In a particular case the *Streptococcus pyogenes*, when injected into the peritoneal cavity of an animal, was not taken up by the cells present; when into this animal the *Proteus vulgaris* (a non-pathogenetic organism) was also injected, the last-named bacteria were readily taken up; thus, the cells, having two organisms presented to them, took up one variety and rejected the other. No physical explanation can be given of such phenomena, and especially of the transformation of an indifferent attitude into one of active response as expressed by attraction. The questions involved have never been exhaustively dealt with, but certain inquiries have been directed towards the factors influencing such movement, the reality of its occurrence being assumed. In discussing the mechanism of immunity against swine erysipelas in the absence of Pfeiffer's phenomenon, Metchnikoff (237, p. 324) quotes experiments of Gengou to shew that besides immune body and complement something else is required in order that phagocytosis should occur. The amount of heated immune serum complemented by fresh guinea-pig serum necessary to protect a mouse against fatal infection with swine erysipelas was determined. A fatal dose of the bacteria was kept in contact with the immune serum and complement for a time sufficient for absorption of the immune body by the bacilli to occur. The bacilli were then washed free of serum, and when injected caused death. From this Metchnikoff concludes that

"it is not the fixateur adhering to the bacteria which determines the protective action of the specific serum. The liquid must in addition contain another substance, and it is this in reality which stimulates the phagocytes." It is evident that this experiment is difficult to interpret, especially as no details are given. In the first case, where death did not occur, not only immune serum but a complementary serum was injected; these serums, of course, contained other bodies besides the actual immune body and active complement; in the second case, on the other hand, only active immune body and active complement were present, but a complication was introduced in that the serums were only allowed to act on the bacilli during the period previous to their injection. Sawtchenko (305) has brought forward evidence in favour of a view that it is really the immune body (*fixateur*, or *immunisine*, as Sawtchenko describes it) which stimulates phagocytic action. First, a leucocytosis was induced in the peritoneal cavities of two guinea-pigs by an injection of bouillon. Next day into the peritoneum of one was introduced some guinea-pig erythrocytes and also some inactivated serum from a rabbit immunised with guinea-pig corpuscles. Into the peritoneum of the other guinea-pig corpuscles alone were injected. In the first instance rapid phagocytosis of the corpuscles introduced was observed; in the second the corpuscles appeared free in the serum for several days and eventually seemed to pass into the lymphatics. Lastly, there was injected into a guinea-pig's peritoneum some of the same inactivated hæmolytic serum along with some bouillon. A copious phagocytosis resulted, and next day the animal was killed by bleeding. The peritoneal exudation was removed, and the leucocytes present well washed with, and then suspended in, salt solution. To part of the suspension some fresh guinea-pig erythrocytes were added. The leucocytes present had, during the day previous to the animal's death, been subject to the immune body injected, but they had been washed of all plasma which might contain either this immune body or any other substance present in the immune serum, or naturally present in the guinea-pig's economy. In these circumstances it was found that in the suspension in salt solution they were still alive and took up the guinea-pig corpuscles added. Next, to another part of the suspension described a small quantity of fresh rabbit blood was added, in order that in the clotting the guinea-pig leucocytes might be disintegrated, and any substances they contained might thus pass out into the surrounding fluid. The mixture was kept on ice for two days and then centrifuged, and normal guinea-pig serum (to provide complement) and normal guinea-pig erythrocytes were added. The latter were slightly dissolved,—more so than if exposed to normal rabbit serum alone with only guinea-pig complement added. Thus, there was evidence that the leucocytes parted with the immune body they had taken up. Thirdly, the red corpuscles obtained in killing the original guinea-pig were washed and injected intraperitoneally into a fresh guinea-pig, in which a leucocytosis had been produced by a previous injection of bouillon; this was done to determine whether during the

sojourn of the immune body in the guinea-pig's body any sensitisation of the erythrocytes of the animal, such as would take place *in vitro*, had occurred. It was found that the amount of phagocytosis which occurred in such circumstances was insignificant. We gather that Sawtchenko attributes this slight phagocytosis to the fact that the immune body previously injected had been so diluted with the fluids of the guinea-pig's tissues that little or no sensitisation could be observed. Sawtchenko's general conclusion is that the fixateur can determine in two ways the phagocytosis of elements which are not ordinarily taken up. First, by fixateur becoming united to the specific object the latter is modified so that phagocytes are attracted to it instead of remaining indifferent. Secondly, fixateur can be absorbed into the phagocytic protoplasm, and the phagocyte thus acquires positively chemiotactic properties towards substances sensitive to the fixateur. It is evident that the question of the ultimate sources of both immune body and complement is left open. Such facts as those disclosed in the experiments of Gengou and Sawtchenko manifestly only apply to cases in which an immune serum is acting, and neither of these observers has pursued his inquiries further.

The Opsonic Phenomenon.—By far the most suggestive work with regard to the factors concerned in phagocytosis is that in which Sir A. E. Wright (371), in conjunction with Capt. Douglas, follows up his previous researches on the bactericidal action of serums. An important principle adopted in the research is the application of the means of exactly measuring the phagocytic power of the blood devised by Col. Leishman (181), and already described (*vide* vol. i. p. 697). In this method the average number of bacteria taken up by the polymorphonuclear leucocytes *in vitro* in a given time is obtained. In the researches of Sir A. E. Wright and Capt. Douglas the cellular —and particularly the colourless—elements of the blood are separated from the fluid by an appropriate method of centrifugation. The fluid part can be treated at will, and its properties investigated; the phagocytes—washed with salt solution so as thoroughly to remove all traces of the plasma—can be subjected to any desired conditions, and when the period of observation has elapsed their activity can be estimated by Leishman's method. The general line of the investigation was to subject different bacteria to the action of the phagocytes in the presence of serum or plasma derived either from the individual who had furnished the phagocytes or from another. It was found that dealing with an emulsion of *Staphylococcus pyogenes aureus* and corpuscles and serum of the observers themselves, a marked fall in the number of bacteria ingested took place when the serum had been previously heated to 60° to 65° C. for ten to fifteen minutes. The serum therefore contained some constituent which affected the phagocytic capacity of the leucocytes. That this constituent acted on the bacteria and made them the prey of the phagocytes was shewn by the observation that if staphylococci were subjected to the action of the serum, and the

mixture heated to 60° C., cooled, and the bacteria then exposed to the action of the phagocytes, the number of bacteria ingested corresponded to the number taken up when the unheated serum and the unheated staphylococcus emulsion were employed. This capacity possessed by serum Sir A. E. Wright speaks of as its opsonic effect (ὀψωνέω, I prepare victuals for). Besides its susceptibility to heat this opsonic substance or *opsonin* disappears spontaneously when serum is kept. Sir A. E. Wright and Capt. Douglas shewed that similar results could be obtained in a marked fashion with the plague bacillus, the *Micrococcus melitensis*, the *Diplococcus pneumoniæ* (Fraenkel), and with other organisms. They give the following classification of bacteria according to the results of their researches:—(1) Bacteria which are eminently sensible to the bactericidal, bacteriolytic, and opsonic actions of normal human blood-fluids—the *Bacillus typhosus* and the *Vibrio choleræ asiaticæ*; (2) bacteria which are in some measure sensible to the bactericidal action of the normal human blood-fluids, and are eminently sensible to its opsonic action — the *Bacillus coli* and the *Bacillus dysenteriæ* (Shiga); (3) bacteria which are absolutely insensible to the bactericidal action of the normal human blood-fluids, but are eminently sensible to the opsonic action of these fluids — the *Staphylococcus pyogenes*, the *Bacillus pestis*, the *Micrococcus melitensis*, the *Diplococcus pneumoniæ* (Fraenkel); (4) bacteria which are insensible both to the bactericidal and to the opsonic actions of human blood-fluids—the *Bacillus diphtheriæ* and the *Bacillus xerosis*. Especially important is the recognition of the third group of bacteria in this classification. In these cases a bactericidal power is absent from the serum, and an intracellular destruction of the bacteria is alone observed.

The importance of these observations is that they raise the question whether the phagocytic cells are by themselves able to perform a phagocytic function—whether it is not necessary for them to be reinforced from without before the englobing of bacteria occurs. According to Sir A. E. Wright and Capt. Douglas this reinforcing takes the form of a sensitisation of the bacterial protoplasm by an element in the plasma. It is natural that such a view should give rise to discussion. There is no doubt that the conception of sensitisation as put forward by these observers is a novel one. It is probable, however, that the phenomena observed by them had been present in experiments by previous workers though their significance had not been recognised. Thus Denys (83, 84) describes experiments by Leclef to shew that in a mixture of antistreptococcic rabbit serum, streptococci, and leucocytes, *in vitro*, the taking up of the bacteria by the latter was much more marked than when normal rabbit serum was used. If the serums used were fresh it is quite possible that an opsonic action was here responsible for the phagocytosis. If old serum were employed probably the effects were due to some other cause. With regard to the facts concerning opsonins there is little doubt; the results of Sir A. E. Wright and Capt. Douglas have been repeated and confirmed by Drs. Bulloch and Atkin (60), and also by Dr. Dean (79).

Further, Drs. Bulloch and Western (60*a*) believe in the existence of a specificity in the opsonic phenomenon in that the removal from a serum of an opsonin towards, *e.g.*, the *Staphylococcus pyogenes* may not remove the opsonin towards the tubercle bacillus. The main question for consideration is whether the discovery unravels the complexity of particular cases of bactericidal action of the type of the Pfeiffer phenomenon, or whether opsonic action is separate and distinct from the bactericidal and bacteriolytic effects previously investigated; it is to the latter view that Sir A. E. Wright inclines. In support of this opinion appeal may be made to his observation on the thermolability of the opsonic substance which distinguishes it from ordinary immune bodies, and also on the occurrence of opsonic effects in cases (*e.g.* with staphylococcus), in which there is no evidence that substances such as immune body and complement are in action. Again, in support of the special character of opsonins is the apparent impotence of the phagocytes to have any marked action when they are washed free of opsonic serum. This last is a point on which controversy is sure to arise. It is, of course, *a priori*, rather difficult to realise how cells capable of taking up pigment and foreign bodies unaided should for a particular case of phagocytosis require help from without. The cells, however, which have been studied in the opsonic work are the polymorphonuclear leucocytes, and ordinarily these are more active in the taking up of bacteria than in ingesting other foreign bodies. In Sir. A. E. Wright's own experiments a slight phagocytosis was often observed in washed corpuscles treated with a serum the opsonic capacity of which had been destroyed by heat. On the other hand, Löhlein (51), working in Metchnikoff's laboratory, states that he has obtained very definite phagocytosis with washed corpuscles. There can be no doubt that whether the phagocytosis of bacteria is or is not totally dependent on substances in the serum, it takes place much more readily when certain substances are present.

The special nature of the opsonins has been denied by Dr. Dean (79), who adduces experiments to shew that Sir A. E. Wright has attached too great importance to the thermolability of the opsonins. Sir A. E. Wright admits that the thermolability of the opsonins is relative (see Wright and Reid (375*a*)). He has found that, while the opsonic quality of the serum of an ordinary person is markedly thermolabile, there occurs in the serum of persons who have responded to tuberculous infection or vaccination a thermostable opsonin, which he denominates an incitor element, but which does not differ from ordinary opsonin in quality. As the result of his work, Dr. Dean considers that the opsonins are to be classed under Metchnikoff's *fixateurs*, and that they do not differ from ordinary immune bodies. The term "*fixateur*" is certainly used in such an indefinite way by Metchnikoff that it may be made to include Wright's opsonins. The real question, however, is, did Metchnikoff recognise that substances might exist in the serum which not only were capable of preparing the bacteria for phagocytosis, but without

the presence of which phagocytosis was either absent or reduced to a minimum? This is very doubtful. While he admits that in immune animals immune body may escape into the blood-plasma, it is evident that he considers the fixateur and the complement normally to be confined in cells; therefore if they are essential to phagocytosis the taking up of bacteria should occur when any cell containing these substances comes in contact with a bacterium. Now Sir A. E. Wright has shewn that this does not necessarily take place. The subject is beset with much difficulty. We have not sufficient data to determine the ultimate significance of the opsonic phenomenon; it may be a particular manifestation of the reaction operating in bacteriolysis, and a thermolabile and a thermostable element may be concerned in it. We must, however, accentuate the advisability of keeping in view the fact that the properties of the serum differ in immunisations against different infective agents; that, for instance, according to Sir A. E. Wright and Dr. Windsor, the development of immunity against staphylococcus infection is unlike the cases of cholera and typhoid in being unaccompanied by the development of a bactericidal serum. Thus, if the opsonins be of the nature of immune bodies, the question arises of how far and in what cases the complements, with which they act, pass out into the serum when the blood is withdrawn from the body. Before the work of Sir A. E. Wright and Dr. Windsor, doubt had often arisen whether certain antibacterial serums really depended for their action on the presence of definite bactericidal or bacteriolytic principles, especially with regard to the antistreptococcic serum (*vide* Lingelsheim (335)). The search for immune body in it has been unsuccessful (Aronson (4)); and the general view of the French school has been that its protective and curative actions depend on its stimulating the phagocytes to take up the invading bacteria (Besredka (25)). There are other instances in which difficulties have arisen as to the action of immune serums, and the work on opsonins must in these cases stimulate fresh inquiries. In any event, this work is fresh evidence of the probable complexity of the processes involved in immunity, and indicates that not only in different cases may different mechanisms be at work, but that even in the same case different mechanisms may be combined.

If the opsonic quality of the serum be in reality distinct from such actions as these concerned in bacteriolysis, two questions naturally arise. In the first place, since the opsonins are present in non-bactericidal serums, how comes it that the death of bacteria results? The natural answer is that in such cases as we have indicated, the substances concerned in the actual killing of the bacteria must be strictly confined to the cellular protoplasm. Whether they are of the nature of the substances which in other cases act intracellularly we cannot tell. To the second question, what is the source of the opsonins? no answer can be given; but we must be prepared to find that they are not leucocytic products.

Whatever views be held as to the scientific relationships of the work of Sir A. E. Wright and Capt. Douglas to other hypotheses regarding

immunity, the methods elaborated by these observers are of great value for the detection and estimation of a particular capacity of the serum; and further, there is little doubt that during certain immunisation processes changes in the opsonic index in the serum are observable — an increase of opsonic power being specially important. Sir A. E. Wright and Capt. Douglas (373) have shewn that in chronic staphylococcus infections, such as are found in boils and furunculosis, the opsonic powers of the serum towards the bacterium in question are lower than in the healthy man. They have also shewn (372) that the same holds good in certain tuberculous infections. They have found that in each case the injection of the dead bodies of the bacteria concerned frequently raises the opsonic capacity of the serum, and with this rise an improvement in the morbid condition is observed. The rise in opsonic power is not indefinite and the conditions affecting it are still unknown, but there can be no doubt of the existence of this capacity for increase in the opsonic power.

It may here be mentioned in connexion with these therapeutic observations that Sir A. E. Wright uses the term "opsonic index" to denote the percentage of opsonic power of the sick person's serum in comparison with that of the control serum of a presumably healthy person (usually that of the observer himself), which is taken as unity. A difficulty might naturally arise here, because the perfect health of the observer who uses his own serum as a test for comparison must be assumed, but in practice this appears to be relatively unimportant.

Several interesting questions here emerge. For instance, given that the opsonic power of the serum generally is lower than normal in conditions of multiple local bacterial lesions, such as occur in widespread furunculosis or chronic tuberculosis, how is it that the injection of dead bacteria can raise the opsonic content of the blood? It would naturally be imagined, if dead bacteria were capable of stimulating such a change, that the constant death of bacteria in the lesions, which undoubtedly occurs, would furnish a sufficient stimulus to whatever mechanism is responsible for the production of these opsonic bodies. We have seen what difficulties arise in connexion with the passage into the body of intracellular toxins and of the substances giving rise to lytic action, and here again we have a difficulty with regard to opsonic action. The possibility of the formation of opsonins, apart from the wandering cells of the body, is again suggested, and it is conceivable that the passage of the opsonin-stimulating material from the lesions may be prevented. There is evidence that the general diminution of opsonic power in the infections quoted may be due to a using up of the bodily opsonin in the local lesions. Thus Sir A. E. Wright and Major Lamb (375), when investigating the agglutinins present in the bodies of typhoid patients, found that the amount present in the splenic pulp, *i.e.* where bacilli abound, was less than in the circulatory blood in which bacilli do not exist. Similarly, with regard to opsonins, Sir A. E. Wright and Capt. Douglas (373) found that the fluid of pus had less opsonic quality than the blood-plasma.

The Perpetuation of Acquired Increased Phagocytic Capacity.—An aspect of the phagocytic hypothesis to which we have not yet alluded is that relating to the mechanism by which the positively chemiotactic influence developed in phagocytes may be perpetuated in the organism. It is evident that if acquired immunity depends on the possession by phagocytes of powers which formerly they did not manifest, a perpetuation of these powers must be provided for in order to account for an immunity persisting in many cases for years. It is very unfortunate in this connexion that the natural diseases of man in which immunity appears most durable, such as scarlet fever, measles, and small-pox, are precisely those diseases whose causal agents are entirely unknown. It is thus easy to overstate the prevalence of immune individuals as a factor in the sociology of the race. Thus in many human diseases when occurring naturally, such as staphylococcus and streptococcus infections, diphtheria, influenza, pneumonia, protection conferred by an attack is either non-existent or is very short-lived. As a scientific truth, however, the persistence of immunisation is well established. In connexion with a purely phagocytic hypothesis there are several difficulties to be faced. If the influences which transform the indifferent attitude of a leucocyte into a tendency to move towards an invading bacterium are wholly within the leucocyte itself, then the chemiotactic tendency will die with the leucocyte. We do not know the duration of the life of a leucocyte, but we do know that leucocytes are constantly being destroyed in the body, especially in the spleen. This wastage must lead to the phagocytes circulating in the blood at any particular moment gradually disappearing from the body. With regard to the important *microphages* or polymorphonuclear leucocytes, there is no evidence that they possess proliferative capacity, and they are therefore incapable of handing on to their successors in the body any quality which they themselves have acquired in their adult existence. With regard to the *macrophage* circulating leucocytes and the *macrophage* extravascular phagocytes, especially such cells as form the endothelial lining of blood-vessels, lymph-vessels, spleen-pulp sinuses or lymph-sinuses, we cannot speak with any definiteness ; we do not know their life-history. The difficulty of the situation can be sufficiently realised from what has been said regarding the important *microphage* cells. However perfectly phagocytic they may become, there is no mechanism known by which their qualities can be preserved for the use of the body, nor do we know of any mechanism by which effects produced on a few cells of the body can be reflected in a change in the constitution of all the fluids of the body.

In this connexion, however, there is one point, hitherto but little recognised, which was considered in some detail in connexion with the pathogenetic effects of bacteria, namely, that the local chemiotaxis of leucocytes from the vessels in the neighbourhood of a focus of bacterial growth is only a part of a general process which manifests itself in every severe infection, and in which a general stimulation of the phagocytic tissues of the body occurs. We have seen how, in the course of this process,

there is not only a draining of the cells from these tissues, especially from the marrow of bone, but that there is evidence of active cellular proliferation in all parts of the body where phagocytes can be formed. The significance of this phenomenon cannot as yet be realised, nor shall we be in a position to understand it till our views of the part played by actual phagocytosis are less nebulous than they are at present. We recognise that a reaction occurs which not only involves activity on the part of cells whose life-course may be nearly run, as is probably the case with the polymorphonuclear leucocytes, but that an impression is made on the germinating capacities of practically all the phagocytic tissues of the body. This opens up the way for a permanence of function being impressed on the cells, which may not come into functional existence till a long period after the actual infection has elapsed. The diseases in which the general reactive phenomena have been most carefully studied would be classed in the group where actual phagocytosis has been found by Sir A. E. Wright to be extremely prominent; but if the phagocytes play a passive part, it will be difficult to assign to the process a causal connexion with the perpetuation of immunity. It remains to be seen whether it is not precisely in those cases in which actual phagocytosis is essential to the death of the bacteria that immunity is most fleeting. In natural streptococcus infection in man, and also in pneumonia—two of the diseases in question—there is little doubt, as has already been noted, that the immunity acquired is very transitory. Evidence bearing on this point will appear in the section on therapeutics (*vide* p. 171).

Phagocytosis in relation to the Constituents of Serums.—Just as in the case of the antitoxins it was important to inquire as to the probable sites of their formation, so it is natural that the same question, though one of greater complexity and difficulty, should be asked with regard to bactericidal bodies when such are found in the serum. As has been shewn, it is still impossible to be certain of the relative importance of intracellular and extracellular processes in the destruction of bacteria and the rise of immunity. In certain cases the bactericidal substances may be wholly confined to the cells and never pass out into the body-fluids, neither under normal conditions in the body nor in these fluids when they are removed from the body; this may occur in the case of staphylococcus infection, both in a normal and in an immunised animal. A parallel is found in the case of the ferment by which the yeast organism transforms sugar into alcohol. In ordinary circumstances this ferment never leaves the protoplasm of the yeast-cell; it is only by the most thorough trituration and expression under great pressure that it can be obtained in a frankly fluid form (54). Again, in other cases, as with typhoid and cholera, both in the ordinary and the immunised animal, bactericidal substances appear in the serum, and the question arises whether they are also present in the plasma. It is to the source of these substances that our inquiries naturally turn; but the question is at present very complicated, since most of the results available are coloured by the supposition that in every case where

bacteria are destroyed in the body bactericidal qualities appear in the serum, whether or no these qualities have been assigned by the observer also to the plasma. We have no doubt in the cases of cholera and typhoid infections, and also in the cases of hæmolytic serums, that bactericidal and bacteriolytic or hæmolytic substances are found in the serum *in vitro*. It might be thought easy to confine our attention to the work done in relation to these serums, but unfortunately the records are complicated with observations relating to other morbid processes, such as infection by the pyogenetic cocci, which in the light of recent results are exceedingly difficult to interpret. In attempting to give a brief account of the work done we must recognise that very little in the shape of definite knowledge has been attained, and it is very desirable that many of the experiments should be repeated with modern methods.[1] Metchnikoff, as has been pointed out, assigns bactericidal properties when they occur in serums to intracellular ferments (*cytases*) escaped from the phagocytic cells in which they were formed. Generally speaking, the bactericidal bodies are in such a view looked upon as, if not identical with, at any rate belonging to, the same group of bodies as the intraprotoplasmic proteolytic ferments. As we have seen, Metchnikoff was led into this position by the comparative method of his research, in which a consideration of the methods of digestion of food particles by the lower invertebrata led up to the defence against invasion by parasites being correlated with ordinary metabolic activity. Nevertheless, he seems to incline to the idea that there are varieties of fermentative substances acting in the same way towards the same result, for he differentiates between the ferments of the macrophage cells, which he names *macrocytase*, and those of the microphage cells, which he denominates *microcytase*. In dealing with the components of hæmolytic serums we have noted certain difficulties lying in the way of accepting the analogies of hæmolytic action with ordinary proteolytic fermentation. Whatever the nature of bactericidal action, Metchnikoff considers the phagocytic cells to constitute the source of bactericidal elements appearing in a serum. This standpoint has been taken up by many observers, with the view of attempting to harmonise the humoral and phagocytic conceptions of immunity. Dr. Hankin (144), for instance, from experiments with the bactericidal qualities especially of rabbit serum towards the *Vibrio Metchnikovi* traced these qualities to the shedding of material from the eosinophil leucocytes. This he founded on the observation that appearance of an increase in the bactericidal power of the serum was accompanied by an apparent loss of granulation in the leucocytes. These results have been subjected to criticism which, to a certain extent, is justified, since we are not in a position to define the homologies of the eosinophilous cells in the different higher vertebrata, and thus cannot assign functions to these cells as they occur in man on the strength of observations made on another animal. No one, however, can

[1] For a full account of the subject and an excellent bibliography the reader is referred to a paper by Dr. Bulloch (56).

take into account the marked weakness of phagocytic capacity in human eosinophils, and the difficulty of thus assigning them a function in a purely phagocytic scheme, without desiring the question to be reconsidered in the light of modern knowledge. Buchner, who at first looked on the alexic power of the blood-serum as evidence against a phagocytic hypothesis, ultimately (52) came to believe that the alexins were derived from the leucocytes. This opinion was based on the artificial leucocytosis caused by the injection into the pleural cavity of the rabbit of wheat-gluten. Buchner found that when the exudation was frozen and thawed so as to kill and break up the leucocytes, the fluid of the exudate was much more powerfully bactericidal than the blood-serum of the animal. Like the latter, the exudate lost its bactericidal capacity on being heated to 55° C. These results were confirmed by Hahn (140), working with *B. typhosus*, *B. coli*, and *Vibrio choleræ*; and this observer further found that when a hyperleucocytosis was induced in an animal, as can be done by the injection of nuclein, the bactericidal power of the blood-serum towards the *B. coli* was raised. A similar fact was observed in man in the hyperleucocytosis which follows the therapeutic use of tuberculin. Some of the earlier results are interesting from the point of view of the recent work on opsonins (cf. Denys and Leclef (84)). Dr. Ainley Walker (340) observed that during the first few hours after blood was removed from an animal immune against typhoid, a rise in the amount of complement present in the serum was observable, and from this he concludes that the thermolabile element has its origin in the leucocytes of the blood. This is, of course, the view of Metchnikoff, who, as we have seen, holds that complement only appears in parts of the body containing cells capable of undergoing phagolysis. With regard to animals immunised against cholera, Pfeiffer and Marx (280) could not find any evidence that the leucocytes of the blood or of a gluten-casein hyperleucocytosis shewed greater activity in protecting guinea-pigs against a minimal lethal dose of the living vibrios than the general blood-serum. They found that such protective properties were exhibited in the most marked form by the spleen, the bone-marrow, and the lymph-glands. Similar results were obtained for typhoid by Wassermann (346).

In support of this view are the experiments of Gengou (135), who obtained a polymorphonuclear hyperleucocytosis by Buchner's method of injecting gluten-casein into the pleural cavity of the rabbit, the exudate being removed on the day following the injection. If three or four days were allowed to elapse before the exudate was removed, 75 per cent of the cells present were mononuclear phagocytes. Working with *B. typhosus* and the *Vibrio choleræ*, he found evidence that bactericidal action was present in a bouillon extract of the polymorphonuclear cells. No bactericidal action was exerted on *B. coli*, and the extract of the mononuclear cells had no action on any of the bacteria employed. Again, Laschtschenko (179) found that though neither inactivated normal rabbit- nor dog-serum had any marked bactericidal

action on the *Staphylococcus pyogenes aureus*, yet when rabbit's corpuscles were digested with the former and the latter added, then a bactericidal effect was produced; from this he concludes that a substance complementary for an immune body in the dog's serum is contained in rabbit corpuscles. Tromsdorff is of opinion that this can be excreted by the corpuscles while still in a living condition. In opposition to such results, Petrie (270), who, using the gluten-casein method, washed the leucocytes free from serum and ground them up with sand at the temperature of liquid air—a temperature which does not destroy ordinary serum alexin—could not obtain any evidence of a bactericidal power on *B. typhosus* or *B. coli* in the extract of the leucocytes, nor had they apparently any power to complement inactivated cell-free exudate; nor could they complement inactivated typhoid immune serum so as to make it bactericidal to typhoid bacilli. This was true both of ordinary and of immune animals. Further, Petrie could not find any evidence that the cells of the spleen of the rabbit could supply the place of the complement of the serum, or that any complement was present in the spleen, liver, or suprarenals. These results are in agreement with similar experiments of Ascher working with cholera. In the face of these contradictory results it is impossible for us to arrive at any result as regards the probable source of the bactericidal elements when such occur in the blood-serum.

Nor can any more definite knowledge be attained with regard to the sources of the constituents of hæmolytic serums. Metchnikoff inclines to the view that the macrophages are more concerned in the englobment of foreign cells, such as blood-corpuscles, than the microphages, which deal rather with bacteria, although he admits that exceptions occur. Adopting this idea, Tarassévitch (321) investigated the properties of emulsions of the organs containing the *macrophages* in greatest number, namely, the great omentum, the lymph-glands, and the spleen. He found that such extracts were hæmolytic to the red corpuscles of birds. A greater degree of hæmolytic action was obtained if to the mixtures an appropriate immune serum (inactivated by heat) were added. The emulsion thus probably contained a complementary body (macrocytase) with an insufficient amount of immune body. The action of the emulsion was generally lost by heating at 55° C., but Tarassévitch notes that in certain cases a degree of resistance to heat was manifested. These macrophage emulsions had no bactericidal effect, and, on the other hand, emulsions of bone-marrow tested by this author—which would probably contain a greater amount of microcytase—shewed no hæmolytic action. These results have been criticised by Korschun and Morgenroth, who shook the organs up with sand, and centrifuging off the débris used the separated fluid. Three objections are raised: in the first place, when the extract of an organ is hæmolytic the corpuscle-dissolving substances are much more resistant to heat than the constituents of an ordinary hæmolytic serum; secondly, no bodies of the nature of *zwischenkörper* can be isolated by the methods ordinarily employed for this purpose;

thirdly, when injected into animals the extracts do not give rise to the antibodies produced by the injection of the constituents of immune serums. With regard to the heat-resisting qualities of organ-extracts, it may be said that Löwit, working with leucocytes ground up with glass-powder, had obtained evidence that here also the bactericidal substances extracted stood a higher temperature without injury than the constituents of an ordinary bactericidal serum. This result has, however, been denied by Schattenfroh. With regard to the possible relationship of the mononuclear leucocytes to the formation of immune body, Dr. Bulloch (58) made blood-counts in rabbits during immunisation with ox-blood, and at the same time tested the hæmolytic power of the serums. He found that when the immune body begins to appear in the serum there is a rise in the mononuclear leucocytes, and that fluctuation in the number of these cells was correlated with fluctuation in the amboceptor content of the serum.

Though the results of these researches on the possible sources of the constituents of bactericidal and hæmolytic serums produce, on the whole, a very confusing impression, the general result must be to incline to the view that sometimes the cells classed by Metchnikoff as phagocytes have a connexion with the origin of the serum constituents. These cells can manifest in their protoplasm the bactericidal and bacteriolytic processes under consideration, and as there is no reason to suppose that in this particular case the cellular protoplasm acts otherwise than through chemical agents, and as chemical agents are concerned in the two corresponding extracellular actions, it is natural to suppose that the intracellular action depends on the presence of the same substances as the extracellular, and that hence the substances found extracellularly have been manufactured within the cells which manifest the same actions. This, however, can at present be looked on as little more than an *a priori* probability, supported indirectly by certain facts. We are not in a position to say more, and the difficulties of elucidating the problems at issue seem very great. One of these difficulties may be that the substances within the cells may exist there in a preliminary form, as is true of the similar case of the ordinary digestive ferments of the pancreas. This possibility has been recognised by Petrie, but evidence bearing on the point was sought for by him without success. We must ever bear in mind, in connexion with the whole question, that we know nothing of how any of the constituents of the ordinary blood-plasma are formed. In conclusion here, it may be remarked that on the whole question of the origin of the constituents of immune serums Ehrlich and his school are silent. The only reference to the subject is to be found in a remark by Ehrlich, in which he quotes with approval an experiment of Pfeiffer and Marx, in which during immunisation against cholera, at a time when no protective substance was present in the serum, such substances were found in saline extracts of the organs.

Phagocytosis in relation to Immunity against Toxins.—It will have been recognised that Metchnikoff's phagocytic hypothesis is chiefly

based on the investigation of cases of bacterial invasion and of immunity against such invasion. It may be asked what attitude the upholders of the phagocytic hypothesis adopt towards immunity against toxins and towards antitoxin-formation. In speaking of the interactions of toxins and antitoxins we have taken up a position of reserve with regard to the part played by antitoxin-formation in the recovery from intoxication, and we have indicated that if cells sensitive to toxins be looked on as the sources of antitoxin, several antagonistic facts must be accounted for. The most important of these facts is the hypersensitiveness to toxin injection, shewn by Behring to occur in some animals which yet possess a definitely antitoxic serum. Metchnikoff has emphasised the importance of this occurrence when interpreted to mean that cells receptive for toxins may exist in the body of an animal where antitoxin-production is going on notwithstanding the sensitiveness. He looks on it as indicating that these sensitive cells are not the sources of the antitoxin-formation. While not in possession of facts directly bearing on a solution of the difficulties, he draws attention (237, p. 43) to the frequency of leucocytosis in animals subjected to bacterial intoxication, especially when the dose of toxin administered is sub-lethal. He also draws attention to the work of Calmette (66) on the action of atropine on the rabbit. The rabbit is very insensible to the action of this poison, but Calmette found that the hundredth part of a dose, which it can tolerate without effect when introduced into the circulation, will produce marked symptoms if injected intracerebrally. In further experiments he injected a large dose of atropine intravenously, and, after bleeding the animal, separated by centrifugation the red and white corpuscles from the plasma. On injecting moieties of the different elements into the central nervous system of other rabbits he found that the part containing the leucocytes was most toxic. The interpretation put on this experiment by Metchnikoff is that the atropine had been taken up by the leucocytes, and that these protect the other cells of the body. On this analogy he evidently inclines to the opinion that in bacterial intoxication, as in bacterial invasion, the leucocytes probably play a predominant part in recovery, and as immune body and complement are probably produced by phagocytes, it is possible that these also are the sources of antitoxins.

The Phenomenon of Agglutination

So far nothing has been said regarding a phenomenon, often observed during the action of a bactericidal serum, which goes under the name of *agglutination*. This phenomenon can be observed within a few minutes of the introduction of bacteria into an appropriate serum. In such circumstances the individual bacteria are at first uniformly distributed through the fluid, and if they happen to belong to a motile species active movements are exhibited. In a very short time, however, a change is seen, which consists in the bacteria becoming massed together in clumps of varying size, and if the reaction be great in degree no free

bacteria remain. If motility has been present this is no longer exhibited, and, generally speaking, the outlines of the bacterial cells are no longer so distinct as before. This last, however, may be due to the commencement of the bacteriolytic action of the serum. The agglutinative phenomenon has long been recognised as occurring not only with bacteria but with red blood-corpuscles in appropriate serums. In the earlier work on immune serums it was looked upon as an integral part of the bactericidal action, and in many of the papers with which we have had to deal this is the attitude taken up. For the sake of clearness we have not alluded to the observations made, as it is possible that the agglutinating properties of a serum are independent of any others that it may possess.

In his early work on the lysis of the cholera vibrio by an immune serum, Pfeiffer (271, 281, 272) noted agglutination as a part of the phenomenon associated with his name. Attention was not actively called to the importance of the occurrence till after the researches (in 1896) of Gruber and Durham (138) on the properties of cholera and typhoid immune sera, and the subsequent work of Widal on the recognition of the presence of agglutination in human serum as a reason for diagnosing the presence of a typhoid infection. Since that time onwards the problem of agglutination has taken its place with other problems relating to immunity. The phenomenon of agglutination of the causal bacteria of an immune serum has been found to be very common. Thus, in many natural infections besides typhoid fever the serum of the sick individual has the power of agglutinating or "clumping" (as it is often called) the causal bacterium. This is true of many cases of bacterial dysentery, glanders, plague, tuberculosis, Malta fever, and cholera, and also to a certain extent of diphtheria, streptococcus and staphylococcus infections.[1] Agglutination is also a very constant property of the immune serums which may be produced in animals by the various bacteria concerned in these diseases. It can also very constantly be elicited in the various hæmolytic serums.

Agglutination in Normal Serums.—The serums of normal men and animals often exhibit agglutinating properties towards many bacteria. Thus in the case of man, many normal individuals agglutinate the *B. typhosus*, the *Vibrio choleræ*, and the dysentery bacillus. Generally speaking, however, a relatively greater degree of concentration is required for the accomplishment of agglutination than is the case when the capacity for agglutination appears in a sick or immunised animal. The question has arisen as to whether the agglutinins occurring in normal serums are specific for the bacterium agglutinated, that is, whether different agglutinins are concerned in the agglutination of different bacteria. Bordet (37) observed that ordinary horse-serum agglutinated both the *B. typhosus* and the *Vibrio choleræ*. On adding cholera vibrios in sufficient quantity to such a serum and centrifuging, the serum lost its capacity

[1] Considerations of space have rendered it quite impossible to go in detail into the numerous questions raised in connexion with agglutination. Only a general treatment of the subject is possible; on the more special questions the results of Paltauf's work have been accepted, and for further information the reader is referred to his paper (265).

of clumping the cholera organism, but retained the property towards the typhoid bacillus. Similarly on treating such a serum with *B. typhosus* it lost its capacity of clumping this bacillus, but could still clump the cholera vibrio. It thus appears as if a certain specificity existed in the natural agglutinins. Whether the natural agglutinins in a serum which act on a particular bacterium are identical with the agglutinins which may by immunisation be produced in the same animal by injecting the bacterium, is a question which cannot be said to be settled. It may, however, be said that slight differences have been found to exist.

Agglutination in Immune Serums.—What Paltauf has called immune-agglutinins can be produced in animals by the injection of living or dead bacteria. Frequently a very small dose of the infective material will give rise to a serum of high agglutinating capacity. The course of the reaction is that the agglutinative power begins to appear from the third to the sixth day after a single injection, but may be delayed considerably beyond this period. The course of the reaction has been studied by Jörgensen and Madsen. These observers found that for two or three days after injection there was little or no effect produced in the serum; if, however, an animal previously treated and possessing a slightly agglutinating serum was used, then a fall in the agglutinating capacity was usually observed on the day succeeding the fresh inoculation. After the preliminary phase there was a rapid rise in agglutinative capacity till, after four to six days, a high maximum was reached. This was succeeded by a fairly rapid fall, during which in a few days the serum might lose half its potency. After this came a period shewing a gradual progressive fall in agglutinating power. A curious point of great theoretical interest came out in these researches, namely, that if instead of a single large injection of the infective agent a number of small daily injections were practised, the same phases of reaction were observed. There was a maximal effect produced which, however, although the injections were still going on, was succeeded by a gradual fall in the agglutinating power of the serum. Observations of a similar kind have been made by Deutsch. The persistence of the reaction in animals may be observed up to at least a year after a single inoculation, and, as Weinberg has shewn, may also be found in the natural infection with typhoid. Certain observations on the persistence of typhoid bacilli in the gall-bladder long after the patient has recovered, open up the possibility that in such cases there has been in reality a continuance of inoculation with material capable of giving rise to the production of agglutinins. There is also no doubt that very great individual variations may be met with.

The Specificity of Immune-Agglutinins.—The question of the specificity of the immune-agglutinins has given rise to a great deal of inquiry, which has been specially aroused by the observation that the serum of typhoid patients has been sometimes observed to clump the other members of the great group of bacilli which are allied to the *B. typhosus*. The general result has been to establish that even for the comparatively weakly

agglutinating serums which are found in natural infections, and still more for the highly agglutinating serums produced in animals, there is a specificity of action, though the specificity is not absolute. Thus a typhoid serum will often agglutinate the *B. coli*, Gaertner's bacillus, the bacillus of psittacosis, though the action on these organisms is usually much weaker than on the typhoid bacillus. From another aspect the specificity of the reaction can be taken to be so marked that clumping by an immune agglutinin can generally be accepted as evidence that in a doubtful case a particular strain of a bacterium is to be grouped as belonging to the species which gave rise to the agglutinin. There is, however, as Dr. Ainley Walker (336) has pointed out, a specialisation of a serum for the particular strain of the bacterium producing it, in that it agglutinates that strain in a greater dilution than other stains of the same species.

Agglutination in relation to Immunity.—We now pass to consider the question of the relationship of agglutination to immunity. As already pointed out, the agglutinative and bactericidal properties of immune serum were at first supposed to be aspects of the action of one substance. In the course of work on the agglutinating properties of the serum of typhoid patients it was, however, observed that the bactericidal properties of the serum were frequently not proportional to the agglutination. A serum might be strongly bactericidal and weakly agglutinative, and vice versa. Similar facts were observed in other diseases. Direct experiment supported the view that agglutination and bactericidal action in an animal's serum were due to different substances. Gengou (134), working with dogs immunised against anthrax, found that an animal with a serum of great agglutinating power might not be so resistant to infection as one with a weakly agglutinating serum. Further, Brieger and Mayer (48) found that rabbits treated with an extract of typhoid bacilli might exhibit a strongly agglutinative serum, which, however, had no higher bactericidal properties than normal serum. Further investigation has shewn that the action of an agglutinating serum is different from that of a serum in which immune body and complement are present. Speaking generally, we may say that while the development of agglutinating power in the blood of an animal is due to a reaction set up by the absorption of bacteria by the animal's body, that reaction is, though here we speak with great caution, possibly different from the reaction, also caused by the presence of bacteria, which results in the formation of such a substance as immune body.

The Nature of the Agglutination Process.—If we now proceed to inquire what the nature of the agglutination process is, we find there are a number of facts which, while not furnishing a complete explanation of the phenomena, yet throw light on their nature.

The Agglutinable Substance and the Agglutinins.—Nicolle was one of the first to investigate this subject; he killed cultures of the *B. coli* by heat, left the bodies of the bacteria to macerate in the culture medium, and then passed the fluid through a Chamberland filter. On adding to this fluid (which contained only the juices of the bacteria)

a little of a serum capable of agglutinating the *B. coli*, he obtained a granular precipitate, microscopically resembling clumps of agglutinated bacilli. This reaction was specific because it was not produced in similar filtered extracts of other species of bacilli. If powdered talc were present in the mixture of bacterial extract and serum the particles were agglomerated like bacteria, and if typhoid bacilli were treated with the *B. coli* extract they became agglutinable by a *B. coli* serum. The bacterial extract was fairly resistant to heat, withstanding heating to 80° C. without alteration. (Eisenberg and Volk found that the agglutinable material began to be affected at 65° C., but did not entirely lose its power at 170° C.) If old bacteria were repeatedly washed with distilled water they were apt to lose their capacity for agglutination. Nicolle found similar facts to be true of the reactions of other bacteria with their corresponding agglutinating serums. He concluded that agglutination consisted of a coagulation or coalescence of the outer layers of a microbe under the influence of the agglutinating serum. His results, at any rate, pointed to the conclusion that the specific element of the serum could not in all circumstances act on bacteria, but that there was something in the bacterial cell on which the specific action took effect. This opinion has been generally accepted, and this something is usually referred to as the agglutinable substance.

Nicolle's work has been extended by Joos (150), who has adduced evidence for believing that there are two agglutinable substances in the bodies of typhoid bacilli,—differing in their sensitiveness to heat. One has its sensitiveness to agglutinin action affected by the temperature of 60°-62° C.,—this Joos calls α-agglutinogen,—while the other—β-agglutinogen—will withstand this temperature without change for several hours. He also comes to the conclusion that in an agglutinating serum there are two sorts of agglutinins: first, what he calls α-agglutinin, which resists heating to 60°-62° C., and has a more special affinity for the α-agglutinogen; second, β-agglutinin, which has a special affinity for β-agglutinogen, but also combines with α-agglutinogen. Eisenberg and Volk also investigated the properties of the agglutinable substance and of the agglutinins. They have brought forward experiments to support the opinion that if to typhoid emulsions of constant strength there be added serum solutions of increasing strengths, while there is an increase in the absolute amount of serum absorbed, there is a decrease in the amount of agglutinin absorbed relatively to the amount originally present. On the basis of this observation Arrhenius (8) believes that the union of agglutinating substance and agglutinin is reversible, and thus corresponds to what he and Madsen hold occurs in the case of the union of toxin and antitoxin. Eisenberg and Volk also hold that the phenomena of diminished agglutinability in heated bacilli are due to the complexity of their agglutinophore affinities, there being in these affinities a thermostable group which fixes the agglutinin, and a more thermolabile group, changes in which result in the bacilli tending to agglutinate. Eisenberg and Volk have further brought forward facts which they interpret as

shewing analogies with Ehrlich's general views regarding the constituents of immune serums. Thus, they think that bacteria can fix much more agglutinin than is actually required for agglutination, just as we have seen occurs in the relationship of a hæmolytic immune body to its corpuscles. Again, they hold that by heating agglutinins a weakening of the essential agglutinating group takes place, while the group by which the agglutinin is attached to the bacilli may be unaffected. They thus assign to the agglutinins a constitution analogous to that of the toxins, and they would call the weakened agglutinins agglutinoids. They also believe that some of these agglutinoids may correspond to Ehrlich's protoxoids, *i.e.* though by heating the agglutinating group may be weakened, on the other hand, the combining group may be strengthened. While, generally speaking, the work of Eisenberg and Volk tends to bring the agglutinins into line with the other anti-bodies investigated by the Ehrlich school, it is right to mention that many of these results have been strongly criticised by Dreyer and Jex-Blake (89). Thus, in relation to the statement that heating the bacilli diminishes the sensitiveness of the agglutinophore group, the latter observers point out that the diminution of agglutinability by heat is not uniform,—sometimes in an agar culture prolonged heating restores the agglutinability. What is more important, bacteria derived from agar cultures are much more sensitive in this respect than those grown in bouillon. They think a partial explanation may be found in the fact that when agar cultures of *B. coli* (the organism with which they chiefly worked) are used, substances are formed which reduce the velocity of the reaction of agglutination. Similarly, in regard to the observations which Eisenberg and Volk adduce as proving the existence of the agglutinoids, Dreyer and Jex-Blake shew that the phenomena vary according as bouillon or agar cultures are employed, and they are of opinion that, though no absolute explanation of the phenomena can at present be given, the appearances can be partly explained by the occurrence of a considerable retardation of the velocity of the reaction producing agglutination.

The results of Eisenberg and Volk, and the deductions made therefrom by Arrhenius, have also been criticised by Craw (75), who found that the formula given by the latter observer does not apply to the entire range of agglutinin solutions. As in the toxin-antitoxin experiments of v. Dungern, he finds that by adding a bacterial suspension to an agglutinating serum in parts, more agglutinin is removed than when the whole suspension is added at once, and he concludes that here also in the reaction the phenomena of adsorption of substances in the colloidal condition are present. In relation to the part which the colloidal state may play in immunity reactions the possibility must be borne in mind that the apparent amboceptor-phenomenon, the agglutination-phenomenon, and the precipitin-phenomenon (*vide* p. 158) may not in reality be due to the appearance of different substances in the serum of an immune animal, but to different properties being possessed by a single substance.

From the very brief statement of results thus given an idea can be formed of the complexity of the issues at present under consideration.

The Effect of Salts on Agglutination.—A very important observation has been made to the effect that the agglutination of bacteria is closely related to the saline content of the solution in which the reaction is taking place. Bordet (37) shewed that if the salts were removed from agglutinated bacteria by washing with distilled water and centrifugation, and the deposit then shaken up in distilled water, the clumps were re-solved, while if the deposit were treated with sodium chloride solution the clumps were re-formed. Joos (149) has investigated the subject further, and has shewn that typhoid bacilli washed with distilled water, or bacillary emulsions from which the salts have been separated by dialysis, will not undergo agglutination when brought into contact with salt-free agglutinin.

From what has been said it will thus be seen that three elements are concerned in agglutination: first, a sensitive substance in the bacterium (agglutinable substance, agglutinogen); secondly, an active substance in a serum (agglutinin); and thirdly, a suitable saline content in the mixture. The various hypotheses advanced to account for the actual mechanism of the reaction have been reviewed by Joos (149). The chief are those of Gruber, Paltauf, and Bordet. Gruber believes that the bacteria develop a viscosity, which is probably brought about by the agglutinin causing certain substances in the outer parts of the bacterial protoplasm to become insoluble. This causes a roughness of the bacterial surface by which the bacteria adhere to one another. Paltauf considers that agglutination of bacteria is due to their suspension in a precipitate formed by the interaction of the agglutinin on certain substances loosely held in the bacterial protoplasm. This view is based on the observation already referred to, that when the filtrate of an agglutinable culture is heated with the appropriate agglutinin a precipitate occurs. Bordet looks upon agglutination as a simple physical phenomenon in which the bacteria are quite passive. According to this opinion, the action of the agglutinin on the bacterium in the presence of salt alters the molecular relationships of the bacteria to the surrounding fluid and causes agglutination. From what is known regarding the effects of alterations in surface-tensions of particles placed in fluids, it must be said that the probabilities are in favour of Bordet's opinion. In this connexion we would refer to the extremely important work of Dr. Ramsden on the behaviour of solids in the surface layers of solutions and suspensions, the further applications of which will probably be found to throw light on the mechanism of bacterial agglutination.

Natural Immunity

At the beginning of the section on immunity it was pointed out that it was customary to classify the phenomena observed into those of natural and of acquired immunity. As the latter have been considered

at length, we must now turn to the former. We may at once state that as investigation proceeds it becomes more and more doubtful whether it is justifiable to maintain a distinction between the two forms. This is the outcome of the realisation that the apparent differences which have hitherto formed the basis for the distinction are probably rather differences of degree than of kind. That individual differences in susceptibility to infectious disease exist there can be no doubt, as is proved in practically every case where in a series of animals each is inoculated with the same dose of an infective agent. Differences also exist in the susceptibility of races. Thus a brown rat may be more susceptible to an infection than a white. In man much was formerly made of such racial differences; thus the Jewish people were supposed to shew insusceptibility to tuberculosis, the white races to plague, and many negro races to syphilis; but all these examples have been shewn merely to depend on differences in the degree of susceptibility. When we consider the subject from the standpoint of what happens under conditions of what is called natural immunity, this becomes most apparent. Thus the lower animals appear insusceptible to cholera, and man appears not to suffer from cattle plague; but when experiment is substituted for observation, the results are again not so convincing. Thus, to take the case of cholera, we find that such animals as the guinea-pig and rabbit are extremely susceptible to the causal organism when it is introduced intraperitoneally, and when special methods are adopted the guinea-pig even succumbs to infection by the intestinal tract. The application of the experimental method generally has rather tended to demonstrate the relativity of susceptibility. Thus, it has been shewn that sometimes an animal insusceptible to an ordinary dose of a bacterium will succumb when an enormous amount be administered; sometimes an adult animal will apparently be naturally immune while a young individual will succumb to infection; sometimes an apparent natural immunity can be broken down if the metabolism of the animal be upset, for example, phloridzin poisoning in the dog renders that animal capable of succumbing to anthrax. There are, however, a few cases where there seems to be a natural immunity, which appears, so far as observation has gone, to be absolute. Thus Metchnikoff (237, p. 342) instances the case of the scorpion, into which a very large amount of tetanus toxin can be injected without producing any pathological effect, and without any evidence of antitoxin appearing in its serum. It is thus possible that toxins, and possibly also some bacteria, may be simply inert matter so far as the bodily cells are concerned, but it is probable that very many of the cases of supposed natural immunity are merely examples of a very high degree of resistance. So far as the controversies that have raged round the explanation of the phenomena have gone, the questions at issue, and the lines taken in the attempts at their elucidation, have been similar to those concerned in the explanation of the recovery of a susceptible animal from a disease, and in the development of immunity in such an animal. The chief points at issue have been the relative

parts played by phagocytic action on the one hand, and by the bactericidal action of the serum on the other. As the investigation of these special cases of high natural resistance has not thrown any fresh light on the general problems of immunity, it is unnecessary to recapitulate what we have already said. Those interested in the matter may refer to the work of Metchnikoff (237) and of Hahn (141).

The Phenomenon of Precipitin-Formation

Among the numerous reactions which work on immunity has brought to light, we must class that which originates when the serum of one animal species is periodically injected, say intraperitoneally, into an individual of another species. If, after a series of injections, the serum of the latter is added to a sample of serum from the first species a precipitate occurs. The precipitating serum is called a precipitin, and the precipitate which can be produced by it is denominated a precipitum. The fundamental phenomena were early noticed by Bordet (37) in the course of his work on hæmolysis, in which whole blood, *i.e.* containing both corpuscles and serum, was used for injections. Dr. Nuttall (261) has published a work containing a critical review of all that is known on the subject, and also many original observations by himself. We can here merely outline the more important conclusions recorded by him, and must refer the reader to the work itself for details.

The reactions of precipitin have the general characters of those which we have already studied. The general course of the immunisation process seems to resemble what occurs in other immunisations. Dr. Nuttall has obtained important results with regard to the specificity of the effect of a serum in relation to the serum by which it was produced. The general conclusion is to the effect that an absolute specificity does not exist, but that by carefully regulating the experimental conditions a great degree of relative specificity can be established. A concentrated solution of a serum may be precipitated by a non-homologous serum, *i.e.* a serum other than that produced by the blood-serum in question; but, generally speaking, the weaker the dilution in which a serum will be precipitated by another serum, the more likely is it that the latter is the serum homologous to the blood. Bloods precipitated in slightly more powerful solutions will probably belong to animals of species closely related to that from which the causal serum was derived. The strength of the anti-serum solution and the time in which the reaction appears also constitute important factors. The more powerful a serum the greater the number of bloods with which a reaction appears. With regard to the relations of the precipitin in its effects there is no doubt that a quantitative relationship exists between the precipitin and the amount of precipitum formed; but here there is an important point to be noted, that the precipitum may be soluble in excess of precipitin. Precipitins have their activity affected by heat, and evidence has been brought forward to shew that different groups in the precipitin molecule are concerned in fixing it to

the molecules to be precipitated, and in actually causing the precipitation of the latter. Though some evidence has been adduced to shew that in the precipitation process two substances, corresponding to the immune body and complement of a hæmolytic serum, are concerned, later work has failed to confirm this opinion. Precipitin weakened by heat has been called precipitoid, and it has been supposed that, as in other cases, a weakening of the toxophorous group may be associated with the development of an increased combining force in the haptophorous group. As the evidence here, however, proceeds along similar lines to that adduced by Eisenberg and Volk in favour of the existence of pro-agglutinoids, it will be well to maintain the open mind with regard to these pro-precipitinoids which is advisable with regard to the pro-agglutinoids.

The true precipitin appears to be bound rather intimately with the globulin moiety of the crude serum containing it; but here, as with other substances of the same kind, it is doubtful whether a mere association without chemical union exists. The precipitum is, in suitable strengths of the reacting substances, formed instantly, and sinks to the bottom of the fluid from which it is precipitated. It is soluble in dilute acids and alkalis, insoluble in water, and is said to manifest the ordinary reactions of albumins. It has been shewn that anti-precipitins can be produced. With regard to the function which the capacity of forming precipitins exercises in the body, this has probably a relationship to the fact that an animal in assimilating its food has to deal with foreign albumins. Dr. Nuttall says: "Presumably they (the precipitins) serve to protect the body against the injurious effects of corresponding foreign albumins, and more probably . . . to neutralise the specifically foreign character of the albumin introduced, thereby making it forthwith assimilable. This may explain the physiological significance of the phenomenon, and, I might add, is in substantial agreement with Ehrlich's theory as to the functions of the anti-bodies in general." In this connexion it may be remarked that the evidence on the whole is rather against the occurrence of an actual precipitation of albumin when a precipitin meets a precipitable albumin within an animal's body. At any rate, when in the later stages of the production of a precipitating serum the causal serum is injected, precipitation *in vivo* does not occur.

The possibilites of the application of facts regarding precipitins to medico-legal work are, of course, evident. The methods of detecting the source of the blood in blood-stains, or of determining from what animal a particular specimen of meat has been derived, are still largely in the experimental stage, but it is quite probable that their reliability in relation to the objects in view may be substantiated. It may be said in this connexion that Neisser and Sachs (252*a*) have studied Moreschi's discovery of the deviation of complement by a precipitin from the medico-legal standpoint.

Cytolytic and Cytotoxic Serums.—Bacteria and red blood-corpuscles are not the only groups of cells of which individual examples, when intro-

duced into a heterologous animal body, stimulate the production of lytic serums. Other foreign cells will act in like manner. This has been shewn for spermatozoa by Landsteiner (176), Metalnikoff (225), and Metchnikoff (235). Thus Metalnikoff injected periodically spermatozoa from the guinea-pig into the rabbit, and found that the serum of the latter immobilised guinea-pig's spermatozoa in a few minutes. If heated at 56° C. it lost this power, but such heated serum could be reactivated by fresh guinea-pig serum. To this spermotoxic serum an antispermotoxin can be obtained, which, according to Metchnikoff and his pupils, consists partly of an anticomplement and partly of an anti-immune body. This antagonising body can be formed even if the toxin be injected into a castrated animal; and Metchnikoff has insisted that this observation militates against the general hypotheses of Ehrlich on antitoxin formation, the view being that the antispermotoxin could only be formed by the saturation of side-chains in the spermatic cells and the over-production of these side-chains. It is evident that this criticism is met by Ehrlich's allegation that in the case of many toxins, *e.g.* in tetanus in the rabbit, other cells in the body contain side-chains identical with those of the most sensitive cells, and that wherever toxin is fixed there antitoxins can be formed.

Many other cells, when injected into the body of an animal of another species, have been shewn to stimulate the production of serums toxic to cells of their own kind. Thus, leucocytes have been experimented with by Metchnikoff (234), Funk (129), and Besredka (29). In these researches spleen, bone-marrow, and mesenteric glands have been injected into guinea-pigs and rabbits, and serums have been obtained which had the power of dissolving white blood-corpuscles both *intra vitam* and *in vitro.* When injected into the living animal they give rise to toxic symptoms due to the destruction of cells which takes place. The occurrence of this destruction can be watched by withdrawing samples from the peritoneal cavity of the affected animal from time to time. These serums, according to Besredka, are more susceptible to heat than ordinary hæmolytic serums, and entirely lose their action at 55° C. According to this observer also, if small, non-fatal doses be administered, an increase of the number of leucocytes can be observed, and he thinks that thus a stimulation of the blood-forming mechanism occurs. This observation is of great importance, for in dealing with toxins we pointed out that van de Velde has brought forward evidence of the pyogenetic staphylococci producing a leucocyte-destroying poison. This toxin may thus in small doses play a part in the leucocytosis which occurs in staphylococcus infections. The further investigation of the question may thus throw light on the leucocytic activity so common in infection. Besredka also observed that the leucocytosis produced by his leucotoxin was accompanied by the development of an anti-leucotoxin. It is said that a serum produced by the injection of spleen-emulsion has a solvent action on the mononuclear and also on the polymorphonuclear leucocytes, while a serum produced by the injection of the bone-marrow has a special action on the latter only. These results have not been confirmed by Flexner

(122), who found that while injections of splenotoxin and lymphotoxin (originated by injecting emulsions of lymph-glands) affected the tissues producing them, and had little effect on the marrow, a myelotoxin affected not only the marrow but also the spleen and lymphatic glands. Flexner again made the important observation that injections of the cytotoxins produced germinative changes in the susceptible organs. Especially was this true of myelotoxin, the injection of which was followed by a very pronounced increase of the leucocytes and of the leucocyte-producing cells of the marrow. The importance of such observations is very great. Many other cytotoxic serums have been produced; thus Delezénne has obtained serums cytotoxic to liver-cells. These serums cause changes in the liver analogous to those of phosphorus poisoning. By injecting preparations of gastric mucous membrane, Dr. Bolton (31) has produced a gastrotoxin which will cause death, with patches of necrosis and hæmorrhage in the stomach wall leading to ulceration. Cytotoxins have also been produced against nerve-cells, pancreatic cells, suprarenal cells, the syncytial cells of the placenta (causing, it is said, when injected, symptoms of puerperal eclampsia), and thyroid cells. The general facts observed in all cases are more or less similar. In most cases there is evidence of the action of an immune body and complement. In most cases there is a want of specificity in the action of the serums. Thus, v. Dungern shewed that a serum formed by the injection of the ciliated cells of the ox's tracheal membrane not only paralysed such cells, but had a hæmolytic action. Similar facts have been observed in gastrotoxins by Dr. Bolton. In this connexion a very significant observation has been made by Demoor and van Lint (82), to the effect that in certain doses an antithyroid serum did not produce necrosis of the gland but evidence of increased functions. It is manifest that the investigation of these cytolytic serums opens up many most important questions, which, however, have to do as much with the physiology of various organs as with their pathology.

Anti-ferments.—We have already alluded to the researches of Morgenroth (244), in which it was shewn that a serum could be obtained capable of protecting milk against the action of rennet. Observations of a similar kind have been made with other ferments. Thus Achalme (2) has obtained an antitryptic serum, Sachs (298) an antipepsin, and Bordet and Gengou (42) an antifibrin ferment. In the last case the important observation was made that the anti-body was specific for the fibrin ferment of the animal species by whose serum its origin was stimulated. Anti-bodies to certain other ferments, such as steapsin, have also been observed. In this connexion perhaps one of the most significant facts is that the bodily cells in certain circumstances appear to have the power of neutralising ferments produced by other cells. Thus Landsteiner (177) and many others have shewn that extracts made from certain tissues have apparently the power of neutralising tryptic ferment. It is evident that the formation of anti-ferments constitutes a very

significant phenomenon. Its existence is so far a justification for the view that bacterial toxins and ordinary ferments, such as those concerned in digestion, might be classed together in the same group of substances; it has already been pointed out how many points they possess in common, and it must be admitted that this identity of reaction which results in both cases in the production of antagonistic serums is, perhaps, the most striking of all their common characteristics. It is probable that this fresh knowledge regarding ferments may open up new lines of inquiry as to their nature.

Ehrlich's views on the Receptor Mechanism of Cells

Whether the properties of serum separated from blood outside the body do or do not represent the properties of the plasma of the circulating blood, there can be little doubt that the substances present in the serum must represent the means by which protoplasm acts in the body. Whether this action in living conditions takes place within or without the bodily cells is not of such great importance. It is as a contribution to the study of protoplasmic processes that the work of Ehrlich possesses its highest value.

In any general consideration of his results Ehrlich (102, 101) has always placed this in the foreground. His opinion is that all the properties of the serum which have been observed in the course of the investigation of immunisation-processes are seen in their true light when viewed as resulting from particular manifestations of the ordinary normal activities of protoplasm It will be well for us now to look briefly at what Ehrlich's views of these normal activities are. Even in his earliest work (99), which bore on this subject, he conceived that in living protoplasm a centre of special structure controlled the specific and peculiar capacities of the cell, and to this centre were attracted atoms and atom-complexes, not directly concerned in the maintenance of life, but having a subordinate position as being concerned with the activities of the cell. The comparison by Ehrlich of these subordinate molecules to the side-chains often occurring in complex organic molecules of known constitution is, we have always thought, regrettable, as it has tended to alienate the sympathies of the organic chemist, who attaches to the phrase a very definite meaning. Ehrlich certainly used the expression metaphorically, and it is only in this sense that its continued conventional use is justifiable. Ehrlich's opinions are mainly developed from the standpoint of considering how these side-chains are concerned in the provision of food for the use of the cell, though it is plain that they might be extended to include the activities of the cell in providing substances necessary for the use of other cells. In a complex animal organism the food-supply of the cell is brought to it in a state more or less suitable for assimilation, and the question arises of how that food material actually becomes part of the protoplasmic structure. Ehrlich points out that many modern pharmacologists do not look on narcotics, antipyretics,

antiseptics, and so forth, as entering into a true chemical combination with the bodily cells. Such substances merely exist in a sort of solution, or are held after the manner of weak saline combinations. They are not truly assimilated as a part of the protoplasmic complex, like the carbohydrate moiety, which by the action of boiling acid can be split off from albuminous molecules. It must, however, be stated that on account of the difficulties presented in the investigation of the subject great caution must be shewn in accepting such an opinion.

It is only food material, Ehrlich holds, which can be combined in firm synthesis in the cellular protoplasm. According to his view the mechanism by which such a true assimilation is accomplished is revealed by his investigations on immunity. The cause of this is, that the foreign materials used in immunisation-processes are in all probability closely allied in nature to the ordinary food materials of cells. On *a priori* grounds this must be looked on as highly probable, for if we think of the food of the earlier forms of life, especially in relation to the development in the primitive animal organism of the dependence for food on organic material already elaborated from the inorganic, we must realise that the composition of the food of such forms must have closely resembled the composition of the feeding cell. If at that period in evolution (as Metchnikoff (236) has shewn exists in the case of the amœba at the present day), among the closely similar foreign cells ingested, some could react on the ingesting organism and kill it, then we may grant the extreme probability of Ehrlich's position, that the mechanism at work in the taking up of injurious foreign material is the same as that in action in the assimilation of food. This mechanism involves the fixation of the food material. Here we have first to think of food material already fit for assimilation coming in contact with the cell. For its fixation the side-chain of the cell has merely to anchor it; a simple haptophorous group will fix the food-molecule. Such a group Ehrlich calls a *receptor of the first order*—it is a receptor such as in an intoxication fixes a simple toxin-molecule. Such receptors, when over-regenerated in immunisation and cast off, form antitoxin. Next we have to think of food-molecules coming to the cell which require further preparation before assimilation is possible. Ehrlich here conceives two possibilities, based on what is deduced from immunisation-processes. The first of these is that a side-chain exists (attached to the cell in a manner undefined) in which there is a haptophorous group capable of fixing the food-molecule, and another group capable of having a digestive action. This form is designated a *receptor of the second order*, and is supposed to be represented,—detached from the cell,—when agglutinins and precipitins appear during immunisation in the serum. In the case of the former group of bodies the fact that they are capable of becoming attached to such a definite mass as a bacillus, and of acting on that mass without the intervention of any second substance in the serum, is looked on as evidence that where they constituted a side-chain in living protoplasm they possessed similar capacities. But when

food must not only be fixed in a cell, but further acted on before assimilation is possible, another alternative is possible. The side-chain (again attached to the cells in an undefined way) may have two haptophorous affinities, one of which fixes the food-particle, while the second fixes another molecule having the capacity of digesting the food-particle. These receptors are *receptors of the third order*, and are represented free in an immune serum containing an immune body which requires a complement for a lytic action to occur. From the facts which have been related bearing on the multiplicity of the substances which can be attached to cellular protoplasm, it is evident that in many cells a great variety of each kind of receptors must exist, a conception which is further borne out by the complexity and specificity of the antagonising bodies that can be produced; thus red blood-cells, as Ehrlich points out, can fix such different substances as the vegetable toxins ricin, abrin, phallin, the bacterial secretions exemplified in tetanolysin and staphylolysin, the snake poisons, and the immune bodies of lytic serums. Yet while there is often great specificity of the receptor for a particular substance, as is exemplified by the specificity of an antitoxin-molecule for its toxin, there need not be the exclusive possession of one particular receptor by one particular type of cell. It will be remembered that in the guinea-pig the minimal lethal dose of tetanus toxin, when injected intracerebrally, was nearly the same as when injected subcutaneously, while in the rabbit a much larger dose could be tolerated subcutaneously than could be borne intracerebrally; this fact was held to shew that, in the rabbit, receptors capable of fixing tetanus toxin existed in organs other than the central nervous system, while in the guinea-pig the toxin could only be fixed in the nerve-tissue. The presence of identical receptors in different cells is what we should expect if these side-chains are subservient to ordinary assimilation, otherwise the preparation of the food material before it reached the sites of its actual consumption would require to be much more elaborate.

It is evident that such views on the normal activities of protoplasm are of a highly speculative character, though at the same time the fundamental facts regarding immunisation, on which they rest, become more and more firmly established the further that investigation proceeds. Many interesting points arise in connexion with occurrences which probably have no direct bearing on immunisation-processes. For instance, what is the significance of the *zwischenkörper* and of the agglutinins, which, as we have seen, are often found in the serum of normal animals. Are these subservient to cellular nutrition, and why do they appear free in the serum?

There is another aspect of the question which ought not to be left out of account. Whenever protoplasm dies it becomes the prey to bacteria. The absence of such bacterial activity in living protoplasm may not be due to a mere absence of proper pabulum for bacterial nutrition. It may in reality follow on a killing of bacteria, or on a neutralisation of bacterial action constantly going on in the living body. The phenomena of

recovery from disease and of artificial immunisation may be only special examples of a process constantly at work.

Finally, there is a phenomenon which in this connexion must be accounted for, namely, what Ehrlich (100) calls the *horror autotoxicus.* If cells, *e.g.* red blood-corpuscles, withdrawn from an animal are re-introduced into its own body, the mechanism which would come into the operation if the cells belonged to another animal species, and even to another individual of the same species, is usually held in abeyance. Only in one case did Ehrlich, working with an animal's own red cells, obtain evidence of the development of what he calls an autolysin, namely, a serum capable *in vitro* of hæmolysing the animal's own corpuscles. A capacity for the ready development of such substances might, it is plain, be fraught with serious consequences, and the absence of such capacity constitutes an interesting problem. That the opportunity for such autolysin development must frequently occur is evident from the fact that cells are constantly being destroyed in the body, a good example being the destruction of red blood-corpuscles by the endothelial cells of the spleen. Either there must be such an individuality in the receptors of the individual that fixation of cells does not take place, and thus over-regeneration cannot occur, or there must be some mechanism which regulates the action of an autolysin. From the fact that, as we have just said, lysis of one cell in another occurs, the latter alternative presents the greater degree of probability. This is further shewn by Metalnikoff's observation (225) that although the intraperitoneal injection of an animal's own spermatozoa produced a spermotoxic serum, the spermatozoa in its testicle were unaffected. Regarding the nature of the regulating mechanism we cannot speak definitely. There might be the development of an anti-autolysin, though no evidence has been obtained of the existence of such substances. The regulation might be due to the occurrence of an auto-anticomplement, which restrained the action of the autolysin by preventing its being complemented. In one case under experimental conditions Ehrlich found evidence for the existence of such bodies, but it is doubtful whether they are formed under normal conditions in the body, and on the whole the problem must at present be held to be unsolved.

The Receptor Mechanism in relation to certain Problems of Infection.—Ehrlich's view regarding the relation of cell receptors, fixed and free, with haptophorous groups in foreign organic material, raises certain points regarding the mechanism of immunity which can only now be discussed. The first of these that we will consider is this: taking for granted that immunity depends on the development of properties in the serum of an animal, and not on the phagocytic activity of cells—an assumption we have very grave reasons for doubting—how is it that on Ehrlich's receptor hypothesis the serum can ever come to have free receptors in it. If the foreign red cells are placed in an animal's peritoneum, their being taken up by phagocytes is not an essential condition to the development of immune body in the serum,—how comes that

immune body into the serum? It is difficult to see how this may occur, unless the mere contact of a red cell with a cell containing a suitable receptor causes this receptor to become detached from the cell. This, however, is possible, for Professor Muir (251) has shewn that if fresh red cells be brought in mere physical contact with cells to which an excess of immune body is attached, the latter give up some of the immune body to the receptors of the fresh cells. Another possibility is that all amboceptors developed in immune serums are really represented by very minute amounts of *zwischenkörper* occurring normally in the serum. It has been shewn that when a *zwischenkörper* specific to certain red cells exists naturally in a serum, and an immune body is developed in the same serum by the injection of these cells, then the amboceptor of the immune body may not be the same amboceptor as that naturally present in the serum. But evidence has never, so far as we know, been sought for in the existence of very minute amounts of *zwischenkörper* in serums; if these occurred, the development of large amounts by the injection of susceptible cells might be explained. The injection of the cells would deprive the serum of its natural content of the particular amboceptor, a steep gradient would be formed between the cells producing the amboceptor and their surroundings, and more amboceptors would pass out. That such an idea is not fanciful is indicated by the work of Friedberger (128), who has shewn that when during a hæmolytic immunisation an animal is repeatedly bled to a moderate extent, the content of the serum in immune bodies is very much greater than in a control animal subjected to identical conditions of immunisation, except that the bleeding has been omitted. It is thus possible to conceive an explanation of the development of immune serums without at any rate a preliminary phagocytic action.

A second point here has to do with the great complexity for which the existence of a receptor mechanism may be responsible, when a reaction between bacterial cells and the cells of the invaded body takes place. Dr. Ainley Walker (337) has shewn reason for supposing that the typhoid bacillus, when grown in its own immune serum, shews an increase in virulence towards guinea-pigs, as proved by its killing an animal with a smaller dose than formerly. This he explains by supposing that in the presence of immune body a process takes place in the bacterium precisely analogous to what occurs in a susceptible animal cell during immunisation. The bacterial side-chains are saturated with the amboceptor of the serum, and this saturation leads to the habit of over-production, so that the bacterium in the course of a few generations comes to possess greater affinity for bacterial cells, and thus greater virulence. To this latter aspect of Dr. Walker's contentions we shall revert presently, but it is plain that the possibility of a bacterium becoming immunised to its own serum opens up a wide field of speculation. Prof. Welch (355) has put forward the idea that certain bacterial anti-bodies are capable not only of neutralising the immune body of the host but, with the aid of complements, of also poisoning the cells of the host. The production of these anti-bodies may be stimulated by the presence in

the host of material not necessarily toxic to the bacteria, as the immune bodies indirectly are. All that is necessary is that the stimulating substances should have molecular groups capable of combining with the bacterial receptors, and that these receptors when over-reproduced in the bacterium should be complemented in the body of the host. The possibility of such occurrences has been suggested to Prof. Welch largely by the results of Flexner and Noguchi (123), in their work on the hæmolytic action of snake venoms. These observers have shewn that if washed corpuscles be subjected to the action of venom no hæmolysis takes place, but that hæmolysis occurs if the serum from which the corpuscles have been separated be now added. In other words, an amboceptor in snake venom links up a receptor in the red blood-corpuscle with a complementary body in the serum surrounding it. In no case have they obtained evidence of the existence of a complement in the venom itself. In certain cases they suspected that the complementary body was contained within the corpuscle itself, and the existence of such an endo-complement has since been proved by Kyes for cobra poison. There is thus some ground for a search being instituted for the occurrence of similar phenomena in infection and also in other forms of disease.

The third point to consider here is the possible bearing of a receptor mechanism on a hypothesis of the virulence of bacteria. Pfeiffer and Kolle (278) shewed that a given amount of typhoid immune serum caused lysis *in vivo* of a very much larger number of non-virulent than of virulent bacilli, and Pfeiffer (275) has brought forward evidence of a similar kind regarding cholera. Generally speaking, the evidence points to virulence in a bacterium being associated with the possession by it of a great number of receptors capable of fixing immune body. Thus, in infection a comparatively small number of bacteria might use up all the resisting material capable of acting on them, and the way would be opened up for free multiplication. Again, Dr. Walker (337), in connexion with the immunisation of bacteria to immune serums, has applied Ehrlich's hypothesis to the explanation of such facts, especially in relation to a possible explanation of chemiotaxis. His view is essentially a broad application of the fact that certain cases have been observed where, working with a simple saline solution, it has been found that a weak solution will attract a living organism which a strong one will repel. If then an affinity may be supposed to exist between receptors in bodily cells and receptors in bacterial cells, and if there be an excess of receptors in the cell over those in the bacterium, the excess may be a determining factor in the exhibition of a positive chemiotaxis. The bacterium will be taken up by the cell and will then, on the Metchnikoff hypothesis, meet complement and be dissolved. If, on the other hand, the receptors of the bacterium be in excess, a negative chemiotaxis will be originated, and the organism will be free to multiply. Its virulence will thus depend on its receptors being in excess. Such a view would explain the development of immunity through increased phagocytosis: the latter would depend on the increase in the number of cellular receptors

present. The hypothesis is very suggestive, and deserves further attention.

A final point here is that the receptor hypothesis of immunity would explain how a bacterium can give rise to immunity independently of the poison it may contain. We have seen the difficulties that exist in connexion with immunity against living bacteria not conferring immunity against the intracellular toxins. It is evident that the receptors causing immunity need not necessarily have any relationship to such toxins.

"Ultramicroscopic" Infective Agents

By ultramicroscopic infective agents are only meant infective agents which are invisible to the highest powers of the microscope at present available. In the cases of several diseases facts have been observed which apparently can only be understood on the supposition that such minute living things exist; great caution is, however, necessary in accepting this interpretation. The evidence chiefly rests on experiments in which a virus has been found to pass through an earthenware filter capable of keeping back ordinary bacteria; such filters vary in the fineness of their pores, the finest being the Kitasato and the Chamberland "B" patterns, the Chamberland "F" pattern being not so fine. Thus in pleuropneumonia in cattle, Nocard (257) found that if the pleural effusion were mixed with water and passed through a Chamberland F it was still infective, but if passed through a B filter or one of Kitasato pattern it lost its infective power. The case of this disease forms a link with diseases whose origin is definitely bacterial, for in the exudate Nocard observed minute refractive particles which could be just seen with a magnification of 2500 diameters. Tartakowski and Dschunkowski (322) have confirmed Nocard's observations, and have found with a magnification of 1000 diameters what they consider to be groups of these refractive bodies. They also obtained cultures of the same by enclosing culture media in collodion capsules, and placing these for two or three weeks in the peritoneal cavity of the rabbit. Propagation through about six generations was thus obtained.

Loeffler and Frosch (186) made similar observations on foot-and-mouth disease. They found that lymph from the vesicles which form in the mouth of the diseased animal, still remained infective after passing through a Berkefeld filter. The efficacy of the filter was controlled by its being found competent to hold back a very small bacillus used as a test. Here the microscope failed to reveal any particulate bodies in the filtrate. Loeffler (185), however, found that, if the infective lymph were passed through a Kitasato filter, it lost its infective power. It was further found that a definite degree of immunity could be established against the disease by inoculating animals with an infective lymph which had been allowed to stand for several weeks in contact with the serum of an animal that had successfully passed through an infection with the disease; curative serums have also been elaborated. In South African

horse sickness Sir J. M'Fadyean (192) found that the diluted blood of an infected horse could pass through a Chamberland F and retain its infective character. Further, if a horse were inoculated with the filtrate and developed the disease, its blood, if filtered, was again infective. The efficiency of the filters has been controlled in the same way as that practised by Loeffler and Frosch. All these observations point to the existence of a group of excessively minute centres of activity capable of progressive increase. It might be urged that the observations could be explained by a toxin action, but this is unlikely. We do not know of any toxin which can increase in amount in a medium apart from the vital activity of cells producing it, and such an increase appears to have occurred in Sir J. M'Fadyean's experiments when a second horse was infected from the filtered blood of the first. Every known toxin produces per unit of volume a definite toxic effect—less will produce less effect and more will produce more. We know of no toxin which will act like sulphuric acid on alcohol, where ether is produced as long as any alcohol remains. We thus must conclude either that the observations on these diseases are explained by the existence of ultramicroscopic forms of life, or that an action is present to which no parallel exists among the phenomena of infections regarding which more is known. The observation by Nocard of what are probably very small bacteria, is in favour of the former alternative. From the human standpoint the observations are interesting in connexion with yellow fever, the virus of which probably passes through an earthenware filter without losing its infective power (see Reed (286)).

Infection by Protozoa

In our discussion of infection attention has been confined entirely to conditions set up by bacterial activity. The work of recent years has, however, revealed the importance of other living agents in producing disease in man and the lower animals. The most familiar example, of course, is found in malaria, the protozoan origin of which is indubitable, and if, as is likely, it be established that relapsing fever, sleeping sickness, and syphilis—to mention only a few examples—have a similar etiology, it is evident that in the future considerable attention must be paid to the general features of the non-bacterial infections. The question naturally arises whether it is possible to trace resemblances between the pathogenetic effects of the bacteria and of the protozoa. In this connexion it is interesting to consider that from analogy syphilis has always in modern times been classed with infections of definite bacterial origin, and it is very suggestive how closely some of its lesions resemble those in chronic glanders. In the cases of malaria and of other similar infections similarities are more difficult to trace. In malaria itself the disease effects are dominated by the destructive processes set up by the development of the parasites within the red blood-cells. The anæmia which after repeated attacks manifests itself, though a most important factor,

must after all be looked on as a secondary manifestation of the disease. Of much more importance from the standpoint of the general pathology of infection is the fever, of which there is as yet no explanation, and the behaviour of the reactive cells of the body. With regard to the rise of temperature, this in a simple tertian case seems to coincide with the entrance of the enhæmatospores into the blood-corpuscles, but whether it is due to a toxic process or to a metabolic disturbance cannot be decided. With regard to the cellular reactions, it is to the condition of the blood that naturally we first look. Here Dr. Stephens and Lieut. Christophers (317) have shewn that during the apyrexia, while there is a diminution of the total number of leucocytes, the large mononuclear cells shew an increase relatively to the other forms, so that they may outnumber the polymorphonuclears ; during the pyrexia the proportions regain the normal. This mononuclear reaction has been also observed by other workers. Its significance is as yet obscure, but it may be remarked that it is accompanied by a reaction in similar cells, especially in the liver and spleen. There is some difference of opinion as to the part played by phagocytosis in the disease. There is no doubt that leucocytes carrying pigment are constantly observed during the paroxysm. Whether or not the pigment is derived from the actual ingestion of parasites or red corpuscles containing parasites is doubtful. L. Barker has no doubt that the parasites are taken up by large phagocytic cells in the spleen-pulp, by the endothelial cells of the splenic pulp, and also by endothelial cells in the capillaries and by Kupffer's cells in the liver. With reference to the taking up of pigment by leucocytes, Barker found that, speaking generally, it is the polymorphonuclear cells in which this is observable, while the taking up of the parasites is rather characteristic of mononuclear cells in the situations stated. As Barker's results were obtained before the precise relationships of the different life stages in the parasite to one another were thoroughly worked out, it is difficult to appreciate their precise significance from the standpoint of phagocytosis being a possible factor in the struggle of the body against the disease. The subject is well worthy of further attention.

If we turn to trypanosomiasis in man we again find evidence of disturbed metabolism resulting in fever and of a mononuclear reaction of a special type in the blood (Manson and Daniels (205)) ; and here also there is evidence of a proliferation of similar cells in certain parts of the body, notably, as Drs. Low and Mott (188) have shewn, in the perivascular lymph-spaces of the vessels of the cerebral cortex. The evidence of phagocytosis is here more difficult to adduce, though some appearances may indicate that such a process is going on.

In the febrile disease known as kala azar, with which in all probability another trypanosome, as described by Col. Leishman and Major Donovan, is associated in causal relationship, phagocytosis has been observed by Sir P. Manson and Dr. Low (206) to take place in the spleen. In relapsing fever, which recent research inclines to place among the protozoan diseases, the important part played by the spleen has

long been known, and the phagocytosis in that organ of the spirillum Obermeieri has been observed.

There are thus in several protozoan infections features which link their pathological effects to those of bacterial disease. Especially is this the case with regard to the phagocytic phenomena we have observed, though we are still far from being able to realise the significance of the phenomena. It is natural, in the light of what we have seen with regard to bacterial disease, that we should think of such an occurrence in its relation to recovery from the disease. No doubt such a disease as malaria can be recovered from, but we have no definite knowledge as to the conditions which determine this event. It is natural also that we should think of the reaction of phagocytic cells in relation to the possibility of immunity being developed against such disease, but here again we cannot dogmatise. Koch (161) considers that an immunity can be developed towards malaria, and bases this opinion on observations made in New Guinea, where he found that often nearly all the children in a village might possess malarial parasites in their blood; the adults did not, and could go to a malarial region without contracting the disease. This cannot be explained by supposing that the insusceptible adults were the survivals of naturally immune individuals. The number of infected children was so great that natural immunity could be said to be practically absent, and Koch is of opinion that an artificial immunity is developed. Quite independently of Koch, Drs. Stephens and Christophers (318) in West Africa had noticed that frequently nearly all the children in a native settlement had malarial parasites in their blood, and further, that the parasites were very rare in children over twelve. These observers speak with caution as to this being evidence of the acquisition of immunity, and, with regard to the question of immunity in general, the same attitude is taken up by Sir P. Manson (204), who rather dwells on the facts of the differences in susceptibility manifest in different races. There is no doubt, in certain cases of Europeans at least, that repeated attacks of the disease do not confer on an individual an increased resistance, but rather the reverse. The facts observed with regard to native children might thus be accounted for by supposing that they possess a high degree of natural resistance. This opinion might be the more acceptable in that the children apparently suffered no inconvenience from the presence of the parasites in their bodies. We must therefore adopt an attitude of reserve towards the whole question of immunity against malaria. With regard to other protozoan infections we have practically no information. With regard to the *Trypanosoma Brucii*, to which a very great susceptibility is manifested, it is doubtful if any immunity can be experimentally produced.

IV. Bacteriology in Relation to Therapeutics

The progress of bacteriology has furnished facts of the highest importance in the elaboration of hygienic measures for the prevention

of epidemic disease. The science has also placed on a sound basis the technique which is the essential of modern surgery. Facts have likewise come to light of great use in the treatment of disease when it arises. The excision of the anthrax pustule, the systematic washing out of the infected puerperal uterus, and even the opening of an abscess, are all expressions of the principle that the mechanical removal of a focus of bacterial growth may be the best method of preventing further inroads by the microbes concerned. In the last case, however, it is by no means certain that we understand all the factors underlying the good results which follow on the adoption of one of the most ancient of surgical operations. Still further, we do not understand why the bathing of the lips of the surgeon's incision with a fluid rich in, it may be, virulent organisms, is not more often followed by a general infection. A similar incision made in a healthy individual and similarly treated would undoubtedly often be followed by the gravest pathological changes. That there are unknown factors at work in such circumstances is indicated by what may occur in the parallel case of plague. Here it has been stated to be questionable whether the insertion of a hypodermic syringe into a suspected bubo for diagnostic purposes is justifiable. The withdrawal through healthy tissues of a needle infected with plague bacilli may convert a localised bubonic case of the disease into a general fatal infection.

Putting aside the mechanical removal of bacteria from a site of infection, the progress of bacteriology has brought out certain methods by which bacterial invasion can be prevented, or the results of such an invasion can be combated after it has occurred. In considering these we shall largely confine attention to the scientific principles which may underlie the various methods, and shall leave the consideration of details to the articles dealing with special diseases. We shall first of all deal with the case of bacterial intoxication.

Antitoxic Serums

Practically all the serums which antagonise bacterial toxins have been used therapeutically. Of these by far the most important is the antidiphtheritic serum, but the antitetanic serum has also been employed.

Antidiphtheritic and Antitetanic Serums.—The methods by which antitoxic serums are produced have already been detailed. From the therapeutical standpoint the important condition to be observed is the accurate standardisation of the serum. This is necessary, as the dosage must be reckoned in terms of the immunity unit we have defined. The actual application of a serum treatment to an intoxicative disease must for its regulation depend on empirical data. We cannot have the least idea of the amount of toxin absorbed in any particular case of diphtheria, and thus every case must be treated with the amount of antitoxin found to give the best effect when applied in a large series of cases. So far as diphtheria is concerned, two main principles are well established. In the

first place, the earlier in the disease the treatment is applied the more likely is it to be beneficial; secondly, the more severe the clinical type of the disease, or the later in the disease the treatment is begun, the greater ought the amount of antitoxin employed to be. Both of these principles are paralleled in what is known from actual animal experiments; we have already stated that the longer the time which elapses between the injection of a fatal dose of toxin and the injection of antitoxin the greater is the amount of antitoxin required to save the animal's life. It has been shewn for diphtheria by Behring that in cases in which treatment is commenced after the fourth day of the disease the proportion of recoveries is practically no greater than in untreated cases. In a case suspected on clinical grounds to be one of diphtheria no time must therefore be wasted in waiting for a diagnosis by the cultivation of the bacillus from the throat. Every physician ought to be capable of undertaking the simple microscopical manipulations which, in the majority of cases of diphtheria, will confirm suspicions based on clinical observations, and when bacilli resembling diphtheria bacilli are detected the antitoxin ought to be administered at once in order that its full benefits may be available. The fall of the mortality from diphtheria since the adoption of the antitoxin method of treatment is fully described in the article on "Diphtheria" (Vol. I. p. 1027). It may here merely be remarked, that the brilliant results obtained are largely dependent on the fact that in this disease the causal bacterium originates as its first pathogenetic effect a local reaction which leads to its presence being suspected. Thus, antitoxin can be introduced into the tissues of the diseased individual before much toxin has been formed. The result is that when the latter is absorbed it meets antitoxin, with which it tends to combine; it never reaches susceptible bodily cells.

In the treatment of natural *tetanus* by means of antitetanic serum the case is unfortunately different. In animal experiments the efficiency of the antitoxin in preventing death after inoculation with the bacillus is as great as that of diphtheria antitoxin under similar conditions and in natural diphtheria. In tetanus in nature, however, there is nothing specific in the local reaction to indicate that infection has taken place; and the disease is not recognised till the spasm-producing effects of the toxin absorbed have begun to manifest themselves. By this time a fatal dose of the toxin has, in many cases, been absorbed, as is indicated by the fact that death may occur even when amputation of the limb containing the infected wound has been performed subsequent to the onset of symptoms. The administration of antitoxin must thus depend for its effect wholly on the capacity of the therapeutic reagent to detach toxin from the cells on which it is already acting. With regard to tetanus, we need only say that the impossibility of early recognition of the disease is a sufficient explanation why in this disease the antitoxin treatment has not been followed by any marked lowering in the death-rate. We consider, however, that the treatment should, nevertheless, always be applied. In the course of a very considerable experience of acute

tetanus, we have occasionally seen cases in which the prognosis was of the gravest character, and in which recovery followed enormous doses (especially by intravenous injection) of antitetanic serum. Even in cases which would be classed as chronic it is advisable to give antitoxin, though spontaneous recovery would often occur. The reason is that sometimes, even when the onset of the disease has been delayed and its development is slow, serious symptoms may eventually appear.

These two diseases—diphtheria and tetanus—constitute the cases in which not only has scientific investigations of the conditions of successful therapeutics been most fully followed up, but in which scientific deductions have been substantiated by practical experience. Further, they furnish the simplest and purest cases of bacterial intoxication known. In both cases what threatens life in an animal attacked is the effect produced on the nervous elements of the body; thus, though the tetanus bacillus in many cases produces, in addition to the neurotoxin, a hæmolytic poison, there is no evidence that the latter under natural conditions causes distinctly dangerous effects.

Antivenenes.—It is different with the case of what, from the human standpoint, is a very important group of soluble toxins—namely, the snake-poisons. Here, as we have seen, there is a complexity of pathogenetic effects which must be combated—neurotoxic, hæmolytic, and necrotic. Not only so, but an additional difficulty is presented in the great, though not absolute, specificity which an antivenene manifests towards the venom of the particular snake used in its manufacture. It is thus impracticable in a great snake-ridden country like India to prepare serums specific for every case of snake-bite. The difficulty is being met by immunising the same serum-producing animal against more than one snake. The venoms of the most common species of different genera are employed. Thus in the Pasteur Institute of India the only serum sent out is that of horses immunised with both cobra and daboia venoms. The therapeutic value of such serums has still to be tested, and other factors besides those specified may militate against success following their use. Thus, Major Lamb (174*a*) has shewn reason for suspecting that the amount of poison which a snake such as the cobra injects, if its glands are fully emptied, is probably many times the minimal lethal dose for man. A favourable feature is that apparently it is possible to get an antivenene to act efficiently in a very late stage of the disease. Thus, Noguchi (258) obtained an anti-rattlesnake serum which could save a sick animal when the limit of average duration of fatal illness was nearly reached—and in certain cases even when this limit had been passed before treatment was begun.

The Rationale of Antitoxin Action.—We may here briefly recapitulate the chief points regarding the manner of the action of antitoxin which have been fully discussed under the heading of "Immunity." When an antitoxin is administered early in a case of disease much of its efficacy is undoubtedly due to its neutralising toxin as the latter passes from the focus of infection into the circulation, and before absorption by

sensitive cells occurs. We have seen, when speaking of toxin-fixation, that a poison of this class, when absorbed, rapidly passes out of the circulation, and also that the longer the interval between such a disappearance and the administration of antitoxin the greater is the multiple of the simple *in vitro* neutralising dose of the antidote which must be injected to prevent a fatal issue. This leads to the conception that in such a case the antitoxin must act by detaching toxin from the cells to which it is already fixed. It is easy, on the Ehrlich hypothesis, to speak of the fixation of the haptophorous group of the toxin-molecule on receptors in the protoplasmic molecules of sensitive cells, but this may be a very imperfect description of the reality. Either the toxin, having gained access to the cell and become, as it were, entangled in its protoplasm, is slowly fixed chemically to intracellular molecules, or fixation, though at once commenced, is a slow and probably complicated process, and becomes more complete the longer the molecules concerned are left in contact. Some such conception might explain the necessity for enormous excess of antitoxin being employed in order to prevent the pathogenetic effects of toxin which has been for some time in contact with cellular substance,—if we accept the view that the interaction of toxin and antitoxin is of a chemical nature. On the conception that toxin is entangled before it is fixed, it may be that from the larger size of the antitoxin molecule the latter has great difficulty in entering the cellular molecule; thus, the longer the delay in the antitoxin injection the greater the number of antitoxin molecules that must, as it were, bombard the cell in order that sufficient may get through to reduce the toxin fixed below the minimal amount lethal to the cell. From the observation that an animal can be saved even after toxic phenomena have begun to be manifested, it is more likely that we have to deal with a very complicated fixation process, which even after being partially accomplished can still be undone. How this undoing of the combination between cellular receptor and toxin comes about we cannot say until we have clearer knowledge of the nature of the toxin-antitoxin reaction. If the Arrhenius-Madsen view of this reaction be correct, then we must consider what will happen when the reversible cell-receptor-toxin reaction goes on in the presence of great excess of the unattached cell-receptors, of which we have seen, on Ehrlich's hypothesis, the antitoxin molecules consist. Evidently some of the toxin molecules, on becoming free from the receptor-toxin combination, of which they have formed a part, will become attached to the side-chains of the antitoxin molecules, and thus will no longer be in a position to affect the cell harmfully. It is true that the antitoxin-toxin combination may, in virtue of reversibility, be again broken up, but evidently if the antitoxin molecules be in excess of the cell-receptors, then, if this breaking up occurs, the probability will be that the toxin part will become combined with another antitoxin molecule rather than with a cell-receptor. It is well to bear in mind that often the detachment of a very small moiety of toxin from the cells would turn the scale in favour of the recovery of the latter. If the toxin-antitoxin reaction

be of the nature of adsorption, we must know more of the nature of such phenomena before venturing on an explanation. In any case, our ideas on the subject must for the present be of a highly theoretical character. We have, however, to face the observation that the administration of antitoxin to an animal after toxic symptoms have appeared may prevent the fatal issue which otherwise would certainly occur. Further, all our information points to the conclusion that the toxin-antitoxin reaction is a chemical one, and we are therefore forced to attempt a chemical explanation of recovery in the circumstances named.

The Prophylactic Use of Antitoxic Serums.—In concluding this section we may refer to the prophylactic use of antitoxic serums. This at present is confined to the injection of antidiphtheritic serum, and is usually practised in those who have been or who are being exposed to diphtheritic infection. Undoubted success has followed such efforts to prevent the spread of the disease, and several interesting questions are thereby raised. With regard to the actual prevention of intoxication it is plain that antitoxin circulating in the blood would at once neutralise toxin as it was absorbed from a focus of infection. The important aspect of the phenomena involved is that the presence of antitoxin in the bodily fluids makes it impossible for the bacilli to settle down, and thus prevents the formation of any focus.

Intoxication Effects in the true Infections.—We have seen that probably many of what may be called true infections, in contradistinction to intoxications, present in addition effects due to soluble toxins. Evidence of an occurrence of this kind in cholera is found in the work of Metchnikoff, Roux, and Taurelli-Salimbeni (239) already alluded to. These observers found that an antitoxin could be formed which protected animals against the filtered products of the cholera vibrio. In plague Markl (212) has attempted to counteract alleged toxic effects produced by the *Bacillus pestis* by the use of an antitoxic serum, but not enough is at present known about the true pathology of the disease even to allow us to judge of the attitude to be adopted towards such an effort. In man, cholera and typhoid fever are diseases in which intoxication appears to be a prominent feature, but practically nothing has been done in the way of combating such intoxication by antitoxic serums. In other infections in which the explanations of the several phenomena manifested are more obscure, nothing in the way of internal therapeusis is possible.

Bactericidal Serums

As to the therapeutic applications derived from the immense amount of work devoted to the elucidation of the properties of bactericidal serums there is little to report. While there is little difficulty in obtaining a serum which will protect an animal against inoculation with such an agent as the typhoid or cholera organisms, and which will even have a curative influence, it has not been found practicable to apply to any great extent the method of passive immunisation in the treatment of disease arising

naturally. In the case of typhoid attempts have been made by several investigators, but without any striking success. In dysentery a combination of passive with active immunisation has been practised by Shiga (310) with more success. The cases of the antiplague and antistreptococcic serums we must reserve for special consideration. Many obstacles prevent—in the meantime at least—the utilisation of passive immunisation in the treatment of the true infections. One of these is the difficulty in obtaining antibacterial serums of a high potency such as, on the analogy of the antitoxic serums, we should expect would be necessary for the successful combating of natural disease. The chief reason for this is, as we have seen, that while immune body is readily increased by an immunisation-process, all attempts to obtain a proportionate rise in complement have hitherto been unsuccessful. But there are further reasons which, on consideration of the scientific aspects of bactericidal action, will be at once evident. One of these, which follows on the last given, is that, even if a serum rich in immune body be obtained, still when this is injected into a sick individual his body may not contain sufficient complement to take advantage of the immune body introduced. Further, if future investigation should substantiate Neisser and Wechsberg's deductions, there is a positive danger to an animal in the administration of immune body in excess of the complement available for its utilisation. In such a case immune body, being in excess (there not being sufficient bacteria to take it all up), may anchor a part of the available complement and prevent an important moiety of the latter from manifesting its action through the immune body really attached to the bacteria. But, further, complement may not only be deficient in quantity, but there may be a defect in quality. There is no doubt that an immune body which is capable of saving one species of animal from infection may be inoperative in another species. This fact remains, whatever view be taken of Ehrlich's explanation, that the phenomenon depends on the multiplicity of immune bodies and complements, and the specificity of a particular immune body for a particular complement. Thus, Wechsberg (349) found that usually pigeons possess no complement which can enable them to utilise an immune serum derived from the rabbit for protection against infection with the *vibrio Metchnikovi*. On the other hand, cases are known in which an immune body of one species of animal can be complemented in another species. Thus Shiga, in his work with the *B. dysenteriæ* (311), has brought forward evidence that the immune body of a bactericidal serum produced by the horse can be complemented in normal human blood. In the cases of many serums there is little doubt that a sufficient or efficient complement does not exist in human blood, and for the present this fact limits the application of bacterial therapeutics in the diseases involved. Considerable search has been instituted with a view to finding foreign complementary serums which would for a given animal act in conjunction with foreign immune body. Thus, in the work with the *vibrio Metchnikovi* just alluded to, Wechsberg found for the pigeon that immune body from the rabbit could be complemented

by normal rabbit serum. The effect was, however, not obtained with all individuals. The explanation is either that the introduction of a foreign complement causes such a rapid production of anticomplement that some of the remaining complement is neutralised, or that in the bodily cells there may be receptors capable of fixing complement and thus preventing its action on the invading bacteria. Ehrlich (97) summed up the situation in 1900 as follows :—"From this it appears that in the therapeutic application of antibacterial serums to man, therapeutic success is only to be attained if we use either a bacteriolysin with a 'complement' which is stable in man ('anthropostabile complement'), or at least a bacteriolysin, the 'immune body' of which finds in human serum an appropriate 'complement.' The latter condition will be the more readily fulfilled the nearer the species employed in the immunisation-process is to man. Perhaps the want of success that as yet has attended the employment of typhoid and cholera serums will be obviated if the serum be derived from apes, and not taken from species so distinctly removed from man as the horse, goat, or dog. However this may be, the question of the provision of the appropriate 'complement' will come more and more into the foreground, for it really represents the centre round which the practical advancement of bacterial immunity must turn." This statement may be taken as representing the condition in which matters stand at the present time in the cases of those diseases in which immune body and complement are concerned in bactericidal action. It may be said that Sir A. E. Wright (370*a*) holds many of the antibacterial serums in use to be really bacterial vaccins, *i.e.* they owe any action they possess to containing some of the bacterial poisons originally injected into the animal from which they have been derived.

Antiserums of Unknown Action

We must now proceed to speak of certain antiserums used therapeutically which from their origin and mode of action appear to require special consideration.

Antistreptococcic Serum. — The immunisation of animals against the pyogenetic streptococci is a matter of great difficulty, and the results when immunisation is accomplished are uncertain as regards both degree and duration. This is what might be expected from the data of human pathology. As is well known, an individual may at short intervals suffer from repeated attacks of streptococcic infection without manifesting either temporary or permanent loss of susceptibility. Many animals, such as the rabbit, are singularly insusceptible to streptococci, at any rate to strains derived from human sources. The virulence of the organism can, however, be raised by such measures as *passage*, growth on special media, etc., and when disease conditions are once produced the way is opened up for immunisation processes. But it is always difficult to gauge the degree of immunisation produced by any particular dose of a culture, and thus at almost any stage of, at any rate a prolonged, immunisation an

animal may be rendered most seriously ill, or may die. There is no doubt, however, that a degree of active immunity can be produced; and, further, that when careful immunisation is pursued for from six to eighteen months, there can be obtained from animals, such as the horse and ass, a serum which has in animals both protective and curative properties. Such results have been attained notably by Marmorek (214) and Aronson (5). The strength of such serums may be judged of by the fact that a few milligrammes may, if injected twenty-four hours previous to inoculation, protect a rabbit against 10 M.L.D. of a streptococcal culture, and even if the injection be delayed till several hours after inoculation, death may still be prevented.

Though the accuracy of these observations is undoubted, nothing is known of the way in which the serum acts. There is little reliable evidence that it possesses any definite bactericidal action, though with regard to this point it is most desirable that investigation should be carried out by the more accurate methods applied in recent times to other serums. Both Aronson and v. Lingelsheim (335) hold that there is a slight bactericidal action, but give no details of the experiments on which this opinion is based. Apparently they do not think that any such effect which may exist is sufficient to account for the action of the serum. Bordet (35), who gives more particulars of his methods, is of opinion that the serum does not possess bactericidal properties, does not confer bactericidal properties on the serum of the animal which it protects, and does not have any effect in diminishing the virulence of the streptococcus. Again, there is no evidence of a bacteriolytic effect being present, though slight changes in staining reaction have been observed in cocci exposed to the action of the serum. The only definite effect which the serum has been observed to have on streptococci is that of agglutination (Aronson, Bordet). Aronson has made a few very incomplete inquiries as to the possibility that, as regards its constituents, the serum falls into line with anticholeraic and antityphoid serums. He sought to anchor any possible amboceptor present by leaving the serum in contact with streptococci for a considerable period; but on separating it from the bacteria he could find no evidence that it was less active than before. Hence he concludes that probably nothing of the nature of an immune body is present. In this connexion the experiments of Denys and Leclef (84) may be mentioned. These observers immunised rabbits against the *Streptococcus pyogenes*, and found that, while the serum of fresh rabbits shewed no bactericidal action on the bacteria in question, such an action, though in a slight degree, was manifested by the serum of immune animals. Further, the leucocytes of a normal rabbit had little or no phagocytic action on streptococci; but if these non-potent cells were placed in the serum of an immune animal they manifested great activity and killed the organisms. Again, if the leucocytes of an immune animal were placed in the serum of a fresh rabbit they did not shew any great phagocytic power. These observations may be interpreted in two ways: either as shewing that for a maximum bactericidal effect two substances are in reality necessary, one

present in the immune animal's serum and the other in the leucocytes; or as being evidence of some such opsonic effect as has been found by Sir A. E. Wright to be at work in similar cases. Bordet is of opinion that the serum neutralises the repellent influence exercised by streptococci on leucocytes. It was in this connexion that he made the observations which are brought forward as justifying the idea of the existence of an actual negative chemiotaxis as apart from a mere state of indifference on the part of leucocytes (*v.* p. 137). The effect of the use of antistreptococcic serum, according to Bordet, is to transform the negative into a positive chemiotaxis. An interesting observation by Bordet is that in such a case there usually occurs, a considerable number of hours after inoculation, a sudden local increase of phagocytes—what may be described as a phagocytic crisis. Aronson, while not adopting the view that phagocytic activity is the essential factor in the potency of the serum, is of opinion that in some way the spread of the bacilli from the point of inoculation to the body generally is prevented, and he has brought forward evidence that this really happens.

It might be suggested that the antistreptococcic serums have an antitoxic action. We have no facts bearing on such a view. Recent cultures of streptococci when filtered are usually, even in the largest doses, non-toxic. Whether, however, the bacteria form in the immune body toxic substances of the nature of aggressins we do not know. Such an occurrence would fall in with Bordet's view of the pathogenetic action of the organisms, but no investigations have up till now been made which throw light on the subject. It is thus undoubtedly true that an active antistreptococcic serum can be obtained, but no satisfactory explanation of its action is forthcoming; on the whole the most probable view is that which regards its effect on leucocytes as the important factor.

The serums of Marmorek and Aronson have been widely used as therapeutic agents in severe streptococcic infections in man. The prognosis in any case of such infection is so uncertain that it is very difficult to judge of the results which have been obtained. Certainly no striking diminution has occurred in the mortality of such a common condition as streptococcic puerperal disease, but no doubt cases have occurred in which apparently good results have followed the treatment. We do not know the conditions which limit the application of the serum in animal experiments, and thus we cannot determine in what circumstances in a human infectious disease benefit is likely to accrue. The results of Neisser and Wechsberg at one time rendered it doubtful whether the use of antistreptococcic serum was justifiable, as a harmful effect might possibly follow. As we have seen, there is no evidence that the effect of the serum is due to the presence of immune body and complement, so that this objection may for the present be neglected.

The apparent inefficacy of this serum has led to the rather hostile attitude at present adopted towards its use. According to some the cause of the apparent want of success is due to the extreme variability supposed to be characteristic of the pyogenetic streptococci. There has

always been considerable controversy as to whether all the organisms isolated from so many different inflammatory diseases, and possessing the broad characters associated with the *Streptococcus pyogenes*, ought really to be classed in one species, and from the present standpoint it has been asked whether a serum active against one strain of the bacterium is really active against all strains. Marmorek (215) asserts that such is the case, but his opinion is not based on the observation of identical action in serums generated by different strains, but on the possession by a series of strains of a similar hæmolytic action. Aronson states that his serum was efficient against strains derived from many sources, but van de Velde (331) in an elaborate inquiry came to a different conclusion. This observer immunised animals with different strains, and found that a serum generated by a strain A did not necessarily antagonise a strain B, and conversely. He made the important observation, however, that if both strains were used in the immunisation of an animal, a serum was obtained which was efficacious against both. As a result many "polyvalent" serums have been prepared by the use in the immunisation of the serum-bearing animal of a great many different strains of streptococci derived from different morbid conditions. There is little doubt that such polyvalent serums should be used in cases in which it is considered advisable to administer antistreptococcic serums.

In the immunisation of animals with various streptococci there have sometimes been introduced strains derived from the throats of scarlet fever cases, and the resulting serums have been used in the treatment of that disease (Aronson (6), also art. "Scarlet Fever," p. 463). Any alleged part played by such cocci in the etiology of this infection rests on insufficient data; nothing can be said regarding these therapeutic applications.

Antiplague Serum.—Several investigators have prepared serums designed to combat the action of the *B. pestis.* Of these the chief are Yersin, Calmette, and Borrel (380), and Lustig (191). Yersin used for immunisation the bodies of bacilli killed by exposure at 58° C., Lustig a nucleo-proteid derived from the bodies of the bacilli. The properties of Yersin's serum in protecting animals under experimental conditions were investigated by a German commission under Kolle and others (164). The protection afforded was partial in that, under the most favourable conditions, less than a third of the animals inoculated survived; it was also of short duration, and after a few days all effects had been lost. If the serum were injected after the animal had been infected, a curative effect was sometimes noticeable up to about eighteen hours—if this period were passed the animals died.

With regard to the properties on which any protective action depends, Kolle and Martini (165) have observed, in intraperitoneal infection of animals protected by the serum, microscopic appearances analogous to those presented in Pfeiffer's phenomenon as seen in a similar cholera infection. Markl (213), working on the effects of antiplague serum on plague bacilli *in vitro*, inactivated horse-serum by heat and found it had no bactericidal action; on adding to such inactivated serum fresh rat-

serum a certain amount of bactericidal action was observed,—accompanied microscopically by changes in the bacilli as described by Kolle and Martini. On adding rat-lymph, rich in leucocytes, extracellular microscopic changes could be observed, and also pronounced phagocytosis. In animals Markl observed that a rich leucocytosis occurred when virulent bacilli and the protective serum were injected. The administration of a greater dose,· than the serum injected could neutralise, was followed by an incomplete phagocytosis and a subsequent fatal issue. The phagocytosis seemed to depend on a sensitising action of the serum on the bacteria, for it followed in an intense degree the injection of organisms which, after being left in contact with the serum, had been separated and several times washed. An important point noted was that when a non-virulent culture was injected the bacteria seemed to perish extracellularly without phagocytosis occurring. The antiplague serum has been stated to have no antitoxic properties. Kolle (162) found that the filtrates of young cultures shewed no toxic properties. When the bacilli were separated by centrifugation from young killed bouillon cultures the fluid was found to be toxic, as were also the filtrates of old cultures. But the ordinary antiplague serums had no capacity of neutralising these effects. Further, an attempt to immunise horses by injecting increasing doses of these intracellular toxins was unsuccessful, no antitoxic serum being formed; and the serum of these horses was incapable of protecting animals against infection with living bacilli. We thus see that by an antiplague immunisation a serum can be produced which has a certain protective and a very limited curative power in animals; the cause of these actions is quite unknown.

Antiplague serums have been used both prophylactically and therapeutically in man. The view usually taken is that they may have a slight effect in modifying the clinical course of the disease, and may be of use in conferring a short-lived protection on those who, without having had the previous opportunity of undergoing the active immunisation processes to be presently described, may have to come into contact with plague cases.

Antianthrax Serum.—Both small animals, such as the rabbit, and large, such as the sheep or ass, can be immunised against anthrax, so that ultimately they will withstand very large doses of virulent cultures. The method usually adopted is to commence the immunisation by using the vaccins introduced by Pasteur for the protective inoculation of cattle, and then to follow this up by injecting every few days about 4 M.L.D. of a virulent culture. Such a procedure was adopted by Marchoux. Sclavo (309) improved on this method by first injecting some antianthrax serum previously obtained by such means and then injecting the living bacilli. By this method the first doses of the latter were prevented from having a pathogenetic effect, and the immunisation process could proceed more rapidly and also apparently more effectively. From highly-immunised animals a serum is obtained which (in comparatively large doses) will protect animals against

otherwise fatal infection, and which has also a very definite curative action.

Here, again, the question arises, On what does the action of the serum depend? Sobernheim (315) was unable to detect in the antianthrax serum any degree of bactericidal action greater than that possessed by serum from an unimmunised animal of the same species. Similar results were obtained by Sawtchenko (304). Sclavo made some inquiries with a view to determining if the action of the serum depended in any way on the presence of immune body and complement. He found that his serum, if heated to 55° C., protected rabbits as well as when unheated. This might have been due to its being sufficiently complemented in the rabbits' body-fluids. He therefore produced a rabbit anti-complement, and introduced this serum (heated to 55° C.) along with the antianthrax serum. The effect of the latter was in no way impaired. From this Sclavo concludes that the action of the serum probably does not depend on the combined action of amboceptor and complement. Both Marchoux and Sawtchenko considered that the serum in some way acted on the leucocytes, and that the resulting phagocytosis determined the protective results obtained. Sobernheim, while not finding evidence of such definite dependence of recovery on phagocytosis, thinks that somehow or other the effect of the serum depends, not on a direct action on the invading bacteria, but on an indirect action in the bodily tissues by which the latter are enabled to prevent the spread of the organisms from the inoculation site. He is led to this idea by the large part played by the individuality of the animal on the results produced; a much larger proportion of individuals will not respond to protective measures than is the case with, say, diphtheria or tetanus, in which the curative serum seems to act directly on the pathogenetic substance. The question of the existence of a possible antitoxic action of the serum might be raised. The notably toxic nature of the effects produced in anthrax in man, in whom the distribution of the bacilli is often markedly local, is calculated to accentuate this inquiry, as is also the fact that in Sclavo's immunisation-method the injection of the antiserum previous to the introduction of the bacilli appears to mitigate the local action of the latter. On this point we can, however, say nothing. The anthrax bacillus in ordinary fluid cultures yields filtrates that are practically non-toxic, and with this organism no experiments, analogous to those of Kolle with the plague bacillus, have been performed.

The antianthrax serums of Sclavo and Sobernheim (315) have been extensively used both prophylactically and therapeutically. Sclavo's product has been tried in Italy in the treatment of human anthrax, and Dr. Legge has no doubt of its efficacy. Sobernheim, to protect cattle, has used the method of injecting the antianthrax serum, followed by inoculation of virulent bacilli. He holds, with considerable appearance of accuracy, that this combination of agents confers a more lasting immunity than does the original active immunisation-method practised by Pasteur. It is impossible at present to assign any reason for this

apparent superiority of the combined passive and active immunisations.

Other Serums of Unknown Action.—In some other morbid conditions serums, whose mode of action is unknown, have been used for therapeutic purposes. Among these serums may be mentioned the antipneumococcic serum of Drs. Eyre and Washbourn, the antirabic serum of Tizzoni and Centanni (326), Maragliano's antituberculous serum (obtained by injecting a mixture of tubercle toxins, insusceptible to heat, and some substances present in tuberculous cultures which Maragliano considers to be thermolabile toxins). We may also allude here to the antituberculous serum of Marmorek (217). This investigator considers that in no ordinary culture medium does the tubercle bacillus produce the toxins by which it operates in the animal body, where it is specially subject to the antagonism of cells. He therefore grows it on a serum which is itself antagonistic to one class of bodily cells, namely, the leucocytes. The serum employed is a leucotoxic one derived from an animal into whose peritoneal cavity the injection of leucocytes has been practised. The bacillus is next grown in bouillon containing juices extracted from the liver, an organ which, from its insusceptibility to tuberculous infection, Marmorek thinks must contain some material antagonistic to the bacterium. Having thus allowed the bacillus first to grow in a serum in which presumably inimical substances coming from leucocytes were neutralised, and then, secondly, to grow under conditions in which it might become accustomed to uncongenial surroundings, he considers that the toxins now produced in the cultures will more closely resemble those produced in the animal-body. He uses these toxins to stimulate the production of an antituberculous serum. The serum has been used for the treatment of human tuberculosis, but it is too soon yet to say anything regarding the results.

Active Immunisation as a Prophylactic and Therapeutic Measure

We now pass to consider the prophylactic and therapeutic applications of processes of active immunisation. The earliest artificial immunisation, that of vaccination against smallpox, is undoubtedly to be classed as such an immunisation of an animal species carried out against a disease by means of a pathogenetic agent (of, up till now, unknown character) whose virulence has been lessened by passage through another species. The same is true of the Pasteur method of inoculation against rabies (267), a procedure which has many points of interest. The cause of the disease being unknown, a tissue—the spinal cord—known to harbour the virus is made use of. The cord of an animal in which the virulence of the agent has been raised by passage is chosen as the therapeutic agent. The pathogenicity is very much reduced by drying, the reduction being proportional to the number of days the drying has been carried on. By taking a series of cords of different ages, a series of specimens of the virus of increasing strengths is obtained—material, in fact, for a pro-

gressive immunisation. By the use of these an animal can be immunised against the virus of the strength ordinarily present in a mad dog. This strength is very constant, and is less than that of the most virulent rabbit cords. But the point of great interest is that in the therapeutic application of the method the active immunisation-process in the bitten patient is carried on during, and is completed before the expiry of, the period of incubation of the virus which has been absorbed at the time of the bite —this period being usually forty days. We cannot give an explanation of the phenomenon. The only available fact bearing on the occurrence is that the incubation-period of the virulent virus, to whose influence before the end of the immunisation the treated individual is subjected, is probably for man much shorter than that of the virus inoculated through the bite of the rabid animal. This, however, in no way throws light on the underlying processes, of which no rational explanation can be given, seeing that even the nature of the pathogenetic agent in the disease is unknown (cf. p. 822).

The first important active immunisation carried out with a known pathogenetic agent was the immunisation against anthrax introduced by Pasteur (266) for the protection of cattle likely to be exposed to infection. This essentially consisted of injecting, first, a culture weakened in virulence by twenty-four days' growth at a temperature above that for optimum growth—the *premier vaccin*, and, secondly, twelve days later a culture grown for twelve days at this temperature—the *deuxième vaccin*. The animal could in many cases resist inoculation with ordinary virulent bacilli. As we have seen, this method has been improved on by Sobernheim, who has combined passive with active immunisation.

Protective Inoculation against Cholera.—The next important disease against which a protective inoculation was devised was cholera. Here Haffkine (139) has proceeded by a method analogous to that last described. A culture, the virulence of which has been diminished by growing it in a current of air, is injected, and this is followed by the injection of a culture (*virus exalté*), the virulence of which has been exalted by passage through the guinea-pig. There is a slight local disturbance, and in animals immunity is now developed against infection with ordinary cultures. This method has been widely applied to man in India, and also in Japan, and apparently is efficient against natural infection, though the immunity seems to pass off in about a year. It is difficult to arrive at any conclusion as to the cause of the active immunisation thus obtained. Kolle and Martini (165) studied the properties of their own serums before and after inoculation. They found on injecting serum, taken after inoculation, along with cholera vibrios intraperitoneally in guinea-pigs that the bacteria underwent degenerative microscopic changes and the animals survived. From this indirect evidence they inferred that their serum had, by the inoculation, acquired bactericidal properties. No direct evidence of the presence of a bactericidal action in the serum of vaccinated persons has been adduced; but Pfeiffer and Wassermann (281) state that the serum of persons who have recovered from

cholera shews little bactericidal action, and in fact in this respect differs from ordinary serum. Bordet (34), working with immune serum from the goat, shewed that here there was considerable bactericidal action, and that this was due to the combined action of a thermostable body developed during immunisation and a thermolabile substance normally present in the serum of the immunised animal. In fact, this observation was the starting-point for all the modern work on the action of immune body and complement. Even if further inquiry shews that the serum of an individual inoculated in the ordinary way is bactericidal, the efficacy of inoculation is not explained. Cholera in man is a disease chiefly marked by intoxication—the bacteria being confined to the intestinal lumen. Now Sobernheim (314) has shewn that guinea-pigs immunised in the ordinary way against intraperitoneal infection still succumb to infection by way of the intestine. In these circumstances it might be considered that immunisation developed antitoxic capacities in the immunised animal, but of this there is no convincing evidence.

Antiplague Inoculation.—We have seen that Yersin, Calmette, and Borrel shewed that animals could be protected against plague by active immunisation. The method has been extended by several observers to the case of man when circumstances arise in which he is likely to be exposed to infection by the causal bacillus. The details of the immunisation-processes differ, but in all cases the material injected consists of the dead bodies of plague bacilli or substances extracted from these bacilli. A very slight illness follows, and to judge from the results of Haffkine's (139) method, which has been widely applied in India, not only is the incidence of plague cases less in the inoculated than in the uninoculated, but when the latter are attacked the death-rate is lower. Though the protection thus afforded is not absolute, and though the duration of any resistance developed is probaby limited, there is no doubt that by inoculation methods the ravages of the disease can to an appreciable extent be diminished.

As to the probable nature of the process at work in the body it is impossible to speak, but it may be recalled that Sir A. E. Wright and Capt. Douglas found normal human serum to be non-bactericidal towards the *Bacillus pestis*; and Sir A. E. Wright and Capt. Windsor (377) examined the serum of the first named two years after a Haffkine inoculation, and also found no bactericidal effect present.

Dr. Klein (157) has used for the protective inoculation of animals dried material from necrotic nodules from guinea-pigs dead of subacute plague; according to this observer's view, such material contains special toxins manufactured by the plague bacilli only in the tissues, and he claims for the vaccin greater efficacy than that possessed by the dead bodies of bacilli from cultures.

Antityphoid Inoculation.—The principle of vaccinating animals against the effects of infection with the typhoid bacillus has been extended to man by Pfeiffer and Kolle (279), and independently and much more extensively by Sir A. E. Wright, who in 1897, in conjunction with Major

Semple (376), published the first detailed paper of a series of memoirs on this subject. The method employed consists in using bouillon cultures grown for three weeks at 37° C. and then killed at 60° C. The sterilisation having been proved to be effectual, ·5 to 1·5 c.c. of the fluid is injected hypodermically into the person to be protected. Slight indisposition follows the vaccination, and there can be no doubt that this affords a very definite degree of protection against natural infection. Though in isolated instances no beneficial effect can be traced, there is no doubt from a consideration of large masses of statistics (367) such as those furnished during the South African War (1899-1902), that the incidence of the disease is less amongst the inoculated than amongst the uninoculated. Here, as with plague, the protection is not absolute—not nearly so absolute as in vaccination against smallpox—but even when typhoid fever occurs in an inoculated person, the risk of death is undoubtedly less, and there is evidence that the manifestations of the disease are less severe. The duration of the partial immunity varies; Sir A. E. Wright (366) puts it down as at least three years, but in some cases the period probably is shorter.

Sir A. E. Wright has investigated the scientific conditions of his protective inoculation against typhoid with a thoroughness and exactitude of technique such as have not obtained with immunisation against any other disease. He has thus laid the basis, not only for the elucidation of the special processes at work in this particular case, but for comparisons with the phenomena of other immunisations such as are necessary to the formulation of the principles underlying immunity in general. Amongst the more important results obtained with regard to typhoid inoculation is the fact—observed by the use of a special method (359) of wide applicability—that the serum of most men exhibits a very definite bactericidal action on the typhoid bacillus, and that a definite rise in this bactericidal power usually follows inoculation (364). This increase Sir A. E. Wright denominates the positive phase. In certain cases the rise is preceded by a fall below the bactericidal potency normal to the individual, which he speaks of as the occurrence of a negative phase. The cause of the negative phase is not clear, but it has been observed when the inoculated individual has suffered a greater degree than usual of illness after the inoculation. This shews the necessity for a careful regulation of dosage, the more so that the use of a fairly large dose of vaccin followed by a pronounced negative phase was observed by Sir A. E. Wright in one instance in his own blood not to be followed by a positive phase. The occurrence of a negative phase may, there is some evidence to suppose, indicate an increased susceptibility to natural infection while the phase lasts, and thus it is important to inoculate, if possible, at a period when the individual is not likely for some little time subsequently to be exposed to infection.

With regard to the part played by the bactericidal power of the serum in killing invading bacilli and thus preventing infection, Sir A. E. Wright speaks with caution, as he has found evidence of an inoculation

being still protective at a period when the positive bactericidal phase has come to an end, though of course in the great majority of cases a definite natural bactericidal capacity would remain (the degree of this capacity so frequently present in man must, however, in many cases be insufficient to protect against natural infection). While unable to assign the exact significance, in relation to immunity, of the presence of a highly bactericidal serum, Sir A. E. Wright appears to be of opinion that in a given case of typhoid fever the possession of such a serum augurs well for a favourable issue to the disease. It must be recognised that in typhoid fever the process of the successful combat of the body against infection is a complicated one. While the agglutinating capacity of the serum cannot, as we have already seen, be correlated with the development of immunity, it may act as a subsidiary factor in the killing of the bacteria. Again, we have seen that Sir A. E. Wright, in his work on opsonins, has traced an opsonic effect in human serum towards the typhoid bacillus. All these factors may, together with a tolerance to bacterial toxins, play a part in the resistance of the individual to infection and in the recovery of the individual who is the subject of infection. We cannot at present realise which factor may be the most important. We do not, for instance, know the significance of the constant escape into the general circulation of bacteria from the locally situated main site of pathological change. Such escape does always take place, as is shewn by the constant occurrence of bacilli in the spleen and other solid organs; but we do not know how the escape takes place or whether it is the bacilli in the Peyer's patches, or the bacilli which pass into the body, which are mainly responsible for the metabolic upset characteristic of the disease. We cannot say whether a great tolerance to typhoid toxins or an increase of the bactericidal capacity of the body is in reality the more important.

Antistaphylococcus Inoculation.—In the diseases hitherto considered, the general object of the measures of immunisation which have been devised, has been to develop in a healthy individual a resistance, so that when he is subsequently exposed to infection, either no disease may result or the disease may occur in a mitigated form. The only exception to which this statement is subject is in the case of rabies, in which the natural period of incubation is taken advantage of for applying what is apparently an immunisation-process. Sir A. E. Wright has, however, brought forward evidence that in certain cases in which a definite infection already exists, the resistance of the body to that infection may be increased by an immunisation-process consisting in the injection of dead bacterial cells. The infections in which he has applied the principle are conditions in which the morbid changes are already clearly localised, or, to quote his own words (358), " where we have to deal with localised bacterial invasions associated with inflammation at the site of inoculation. The situation is here entirely different from that which has to be confronted in septicæmic disease. On the one hand, the conditions are here already unfavourable to the invasion of the blood-stream by micro-organisms, and there is, on the other hand, a considerable uncalled-on reserve of resistance on the part of

the organism. We have to deal, in fact, with a situation not altogether unlike that which obtains in the case of already partially immunised animals. . . ." The first series of infections to which Sir A. E. Wright (363, 373) applied this principle were the multifarious manifestations of staphylococcus infection which are presented clinically in forms of furunculosis, sycosis, acne, recurrent boils. In several cases of this kind a very marked improvement has followed vaccination with killed cultures of the staphylococci isolated from the lesions. The success of such treatment, however, wholly depends on strictly following out the general principles laid down by Sir A. E. Wright, namely, that the aim must be to obtain in the vaccinated individual an increased resistance. In doing this it is to be remembered that every bacterial injection may be and often is followed by a diminution of resistance—the negative phase,—that this phase ought in the ordinary course—if the resources of the organism be not overstrained—to be followed by a positive phase of greatly increased resistance, which in turn is followed by a fall from the maximum of this positive phase to a level which is higher than that present before the vaccination. Such a course of reaction represents a successful vaccination. In cases in which, as usually happens, repetitions of the injections are required, these must be practised after the positive phase is well established. They must on no account be given during the negative phase, as a still further drop in resistance would then take place, and this may be accompanied by an aggravation of local manifestations. It is evident, then, that such inoculation-procedures must be controlled by constant observation during the course of the treatment. In the case of staphylococcus infection the observations must be directed to periodic estimations of the opsonic power of the serum. Sir A. E. Wright and Capt. Douglas (373) have shewn that in staphylococcus infections the opsonic power of the blood is less than that of healthy individuals. During immunisation the opsonic index should pass through the phases described, and ultimately become higher than the average normal. With this increase of opsonins in the blood the local infections become less frequent and less severe, and ultimately in many cases completely disappear. With regard to this utilisation of the opsonic index as a test of the progress of an immunisation, we may say that its value as such is not affected by any difference of opinion as to the ultimate nature of the opsonic reaction.

Antituberculous Inoculation. — The introduction by Koch of his second form of tuberculin (which he called "tuberculin-R") constituted quite a new departure in his method for the treatment of tuberculosis. With the original form of tuberculin, as we have seen, the effect produced depended entirely on the toxic action of a bacillary extract mechanically detaching the tissue which contained the infecting organisms. The method of application of the tuberculin-R, on the other hand, was calculated to bring about an active immunisation. The composition of the new tuberculin-R differed from that of the original substance in that it consisted essentially of the disintegrated bacillary protoplasm. The

immunisation-method thus falls into line with the procedures adopted in the cases already discussed. The technique was the usual one of administering at intervals gradually increasing amounts of the bacterial product. The want of success attending the use of the original tuberculin caused the new method to be looked at askance—the more so that there was not a frank recognition of the entirely new principles that underlay the new treatment. The treatment has, however, received a fair trial, though opinion as to its efficacy has varied. Recently Sir A. E. Wright (370), in working at the subject, has taken up the general position that many cases of tuberculosis can be included among the local infections, in which it is possible so to raise the resistance of the organism as to cause the infections present to disappear and to prevent new infections from developing. He has further applied his methods of investigation to the immunisation procedures involved, and has brought forward facts indicating that it may be possible to follow with greater exactitude the effects of the tuberculin injections, and thus to ensure the rejection of cases in which their application is likely to do more harm than good. The great difficulty in the practical application of the new tuberculin has been that in certain cases where it has been injected an aggravation of symptoms has taken place. No means were available by which the effects of the injections could be controlled. An attempt which was made to do so by observing the effects of antituberculous immunisation in developing in the treated individual an agglutinating serum was, as it was bound to be, unsatisfactory, for, as we have seen and as has been recognised in connexion with the prognostic significance of the serum reaction in typhoid fever, agglutination phenomena are not capable of direct correlation with the phenomena of immunisation. Sir A. E. Wright and Capt. Douglas (372) hold that a much surer method of following the progress of an antituberculous immunisation lies in the observations of the opsonic capacities of the serum. Great care is, however, necessary in interpreting such observations. (See Wright and Reid (375*b*).) In tuberculous patients, with the disease in a strictly localised form, the opsonic index is often low. But when the tuberculous process is active then the opsonic index may occasionally be high and is, generally speaking, irregular. In cases of localised tuberculosis treated with new tuberculin the opsonic index is often raised. The characteristics of the reaction following injection are of the same kind as have been observed in other cases. There is the occurrence sometimes of a negative phase, succeeded by a positive phase, sometimes of a persistent negative phase. Sir A. E. Wright (368) points out that it is easier to get an accumulation of negative phases than an accumulation of positive phases, and thus inoculation against such an infection as tuberculosis produces a very different degree of response from what occurs in immunisation against, say, diphtheria toxin. Thus the physician ought to "treat each inoculation as an independent event," to be content with obtaining a simple positive phase, and not to aim at a high degree of immunisation, for this is impossible to attain. It follows that the principle of gradually increasing the doses of the

immunising agent must in the case of tuberculin injections be abandoned, and, as a matter of fact, Sir A. E. Wright uses for successive inoculations only from $\frac{1}{1000}$th to $\frac{1}{600}$th of a milligramme of the tuberculin-R powder—such being a very small dose when compared with those which are sometimes administered. A number of cases have been recorded by Sir A. E. Wright, Dr. Bulloch (58), and others, in which attention to the effect of every particular tuberculin injection practised has been followed by a permanent improvement of the disease manifestations.

We have already pointed out, when speaking of Sir A. E. Wright's work on opsonins, that the characters of the local bacterial infection, as distinguished from the general bacterial infection, must be carefully considered. There is here involved one of the most difficult problems of infection. Sir A. E. Wright has put forward a view to explain why the action of bacteria at one time may be localised and at another general. He does not accept the view of Metchnikoff that the condition of the blood-serum does not represent the condition of the blood-plasma, and he rests his attitude as to the explanation of localisation of bacterial action on the fact that bacteria may multiply in one region of the body when the fluids of the rest of the body are strongly antagonistic to their vitality; he and his co-workers have shewn that the fluids present at the focus of bacterial growth are actually often poor in such antagonistic properties. He and Major Lamb (375) found this to hold good in typhoid fever, in which the spleen, which is a site of active bacterial multiplication, may be specially poor in agglutinins, and similar facts are true of the opsonic capacities of the fluids derived from local manifestations of tuberculous and other infections. The view put forward is that organisms grow in regions where the bacteriotropic pressure is low, *i.e.* where antibacterial substances are either absent or reduced in amount. Bacteria gaining entrance into the subcutaneous tissues of the body will meet, in the lymph, antagonising substances. If such materials are not sufficient to kill the organisms outright, then the latter will absorb what antibacterial substances there are present, and thus render the surrounding lymph deficient in such bodies. The bacteria, not being killed, will multiply, but if they wander beyond the focus, they will come in contact with lymph of higher bacteriotropic pressure, and will be subject to antibacterial influences. There may thus be conceived a focus, in the centre of which, there being no antibacterial bodies, great bacterial multiplication is possible, while at the periphery the antibacterial content of the fluids rises in amount, and is great enough to kill any isolated bacteria which may pass out from the centre. If the peripheral forces are insufficient to kill the bacteria, then a general infection will occur. There may, however, be an ebb and flow in the development of the general antibacterial powers of the body. A temporary escape of bacteria from a nidus—the auto-inoculation of the body—may be followed by a reaction causing an increase, and successive waves of exaltation and depression, as observed in the opsonic index in tuberculosis, may occur. Whatever the explanation, there is in the local

tissue-proliferation around a bacterial focus a zone of resistance which appears concerned in the prevention of the spread of bacterial growth. The existence of a period of about 48 hours of danger after a wound where danger of infection exists is still unexplained, but it is significant that the danger-period ends about the time when granulation-tissue begins to form, and it is significant that even in a susceptible animal anthrax bacilli may be laid on granulation-tissue without infection occurring.

Our reason for introducing these considerations here is on account of their bearing on vaccination against tuberculosis. In this disease there is, according to Sir A. E. Wright, in the tuberculous nidus a deficiency of opsonic power. If the opsonic power be increased, then phagocytosis will occur, and a death of the bacilli will take place. The opsonic power of the body-fluids can often be increased by tuberculin injection properly controlled. The gradient between the general body-fluids and those of the local nidus will be steeper than usual, and thus more opsonin will enter into the nidus with the effect described. But the opsonic content of a nidus can also be raised by stimulating the flow of lymph through the part. This, according to Sir A. E. Wright, probably is the rationale underlying the success of methods which surgery has empirically practised since the earliest times. These include counter-irritation in all its forms, such methods as retarding the flow of blood through a limb, massage, the opening of tuberculous cavities, *e.g.* the peritoneum. A similar process may be responsible for much of the good effects that follow the opening of an ordinary abscess.

With regard to tuberculosis, v. Behring (20*a*), in 1905, announced a new product of the tubercle bacillus which might be used for vaccination. So far as can be made out, this essentially consists of bacilli from which all the toxic materials have been extracted, but up to the present details are wanting.

Vaccination in other Local Infections.—It is plain that the principles discussed are not limited in their applicability to tuberculosis and staphyloccus infections. Sir A. E. Wright (368) has treated cases of local infection by such organisms as the *B. coli*, *Micrococcus melitensis*, and the gonococcus on similar lines.

Artificial Leucocytosis in Prophylaxis.—An artificial leucocytosis can be caused by the injection into an animal of a number of agents, *e.g.* gluten-casein (aleurone), nucleic acid, and even normal saline solution; and as the leucocytes appear to play an important part in the killing of bacteria, it has been suggested that such a leucocytosis might combat a bacterial invasion when such was likely to occur. Mikulicz-Radeski (241) has shewn that an artificial hyperleucocytosis in guinea-pigs increases their resistance to *B. coli* infection, and he has tried the effects of causing such a leucocytosis in man by the subcutaneous injection of about 50 c.c. of a ½ per cent to 4 per cent solution of neutralised nucleic acid. The subjects were individuals who were (twelve hours later) to be the subjects of serious abdominal operations, in which bacterial infection

from an opened gut was possible. The results appeared to justify the procedure, but are at present too scanty to enable us to judge as to the real value of the method.

Conclusion.—Looking at the question of infection as a whole, we have to recognise that its consideration brings us in contact with many general biological questions. It is suggestive that the subject of immunity, with which the subject of infection is so intimately bound up, has led two great observers to the same conclusion, namely, that the behaviour of an infected organism towards the infective agent depends on capacities which normally are concerned with nutrition. Certainly in the future this aspect of the subject must play a prominent part in the investigation both of the properties of cells and of the properties of the body-fluids in an infected animal. In such investigation there must come to light the true meaning to be attached to the expression "the reaction of the organism," which is so often used. At present we can only say that in this reaction stimuli are applied to protoplasmic forces with various results. Sometimes these stimuli apparently result in actual motion, as is probably the case in many motile cells, sometimes the stimuli cause increased chemical activity, sometimes increased reproductive capacity. In the operation of these stimuli there often appear indications of what seems to be a very general principle in protoplasmic activity,—a principle illustrated in muscular contraction,—namely this, that up to a certain limit the response to a strong stimulus is disproportionately greater than the response to a weak stimulus. Finally, we have the phenomenon so frequently observed in immunity procedures, and well illustrated in connexion with the formation of antitoxins, namely, what we may call the effect of the summation of stimuli. Here we have the phenomenon of a series of responses occurring till a maximum effect is produced, and followed by a cessation of protoplasmic activity till a period of rest has intervened. A consideration of infection forms but another instance of the principle that pathological events are to be only understood by a consideration of the general biological principles underlying them. From the standpoint of pathology generally the most important aspect of the modern work on infection is that processes have come to light relating to the interactions of the bodily cells which may shed light on other morbid conditions besides those caused by the invasion of parasitic organisms.

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INFECTIVE DISEASES OF ESTABLISHED BACTERIOLOGY—*Continued*

COMMUNICABLE FROM ANIMALS TO MAN

GLANDERS AND FARCY
ANTHRAX

OF CHRONIC COURSE

TUBERCULOSIS
STREPTOTHRIX INFECTIONS
ACTINOMYCOSIS
SYPHILIS

INFECTIVE DISEASES COMMUNICABLE FROM ANIMALS TO MAN

GLANDERS AND FARCY

By Prof. G. Sims Woodhead, M.D.

Synonyms.—Gr. Μᾶλις or Μηλίς; Lat. *Malleus*, *Equinia*; Fr. *La Morve*, *Le Farcin*; Ger. *Rotzkrankheit*, *Rotz*, *Wurm*; Ital. *Morva* (*Farcino*); Span. *Muermo*.

Glanders, which as a primary lesion has been most fully described in the horse, is a specific infective disease. It derives its name from the presence, in advanced cases, of enlarged glands in the submaxillary and parotid regions; the enlargement of these glands being apparently due to the action of a specific irritant, which, making its way inwards from the surface of the mucous membrane of the nasal respiratory passages, excites well-marked and characteristic lesions in the mucous membrane and in the submucous tissues of these passages, and may extend to distant parts through the lymphatic channels and, more rarely, by the blood-vessels. In almost all cases of glanders the lungs appear to be affected, probably before any other lesion makes its appearance.

Historical.—Although it was not until about the end of the fifth century that Vegetius gave the first systematic description of a malady which he names "Farcinium"—the farcy of more modern writers—Aristotle (*circa* 335-322 B.C.) gave the name μηλίς to a disease in the ass, which commenced with a purulent discharge from the nostrils, and always proved fatal when it extended to the lungs. In the fourth century A.D. Apsyrtus, "a veterinarian in the army of the great Constantine," recommended the segregation of animals affected with a disease, μᾶλις, which he described as appearing under four different aspects—the moist form, the dry, the articular, and the subcutaneous. He recommended segregation of affected animals for the purpose of preventing the spread of the infection of the disease. Modern veterinary authorities point out that along with true glanders he must have included other diseases, as he maintains that μᾶλις was readily amenable to treatment. On this point his opinion was not in accordance with that of his contemporary, Hippocrates, who, although he gives a prescription to be used in the treatment of the disease, described μᾶλις in its advanced stages as incurable.

Although Vegetius, writing later, grouped conditions other than

glanders under his term malleus, of which "he distinguished several different varieties," he evidently included two forms of true glanders—*Malleus humidus*, the glanders of the present day, and *Malleus farciminosus*, our modern farcy. The latter of these conditions he looked upon as curable, but the former, especially when it was characterised by a saffron, yellow, or bloody nasal discharge, as being a very virulent disease, and prone to be fatal. He was firmly convinced of the contagiousness of the disease, and recommended the isolation of all suspected cases as well as of those that were known to be actually suffering from the disease.[1]

Taking a long leap and coming down to the sixteenth century, we find that the contagious character of glanders was then fully recognised on the Continent. Sir Ernest Clarke and Principal Sir John M'Fadyean call attention to a very quaint account of glanders by Fitzherbert in his *Boke on Husbandry*, published in the early part of that century (1523), from which it is evident that this author recognised the contagiousness of glanders and farcy. In France, Solleysel (1667) taught that the infective matter of glanders could be conveyed through the air. Saumier (1734) was so convinced of the infectiousness of the disease that he described most carefully a method of disinfecting stables in which glandered horses had been lodged. Arsault (1741) and Bourgelat (1764) came very near our modern ideas and teaching when they recommended that all animals undoubtedly affected should be destroyed, and that all suspected animals should be carefully isolated. Towards the end of the eighteenth century Abildgaard and Erik Viborg in Denmark and Saint Bel in England laid special stress on the high infectivity of the pus and secretions (and more rarely of the blood (?)) of glandered and farcied animals. Viborg maintained that the two conditions, glanders and farcy, had a common infective agent, and that this agent, though originally highly infective, appeared soon to lose its infective power, especially if it were dried. Early in the nineteenth century Colman and Delabere Blaine—whilst recognising that the pus and secretions of infected animals were possible agents in causing the disease—were inclined to lay far more stress on such factors as imperfect ventilation, bad food, overwork, as playing the leading part in the production of the disease.

The communicability of glanders and farcy to the human subject was not fully recognised, though it appears to have been suspected from time to time, until Osiander, in 1783, stated that the human subject might be affected; and in 1821 Schilling gave a very accurate description of the disease. Again, in 1828, Travers and Colman proved that the disease might be conveyed from man to the horse, and this was confirmed by Elliotson in 1833. Rayer (1837) published most interesting observations on the transmission from the equinia to the human species.

The final proof of the specificity of glanders and farcy, and of the bacterial origin of these conditions, was obtained by Löffler and Schütz

[1] For further history of the disease and for references to earlier authorities see Bass (5) and M'Fadyean (45).

(1882) when they obtained pure cultivations of the *B. mallei* from the lesions of animals affected with these diseases, and with this bacillus were able to produce identical conditions in hitherto healthy animals, from the lesions in which they were again able to isolate the same bacillus in pure cultivation. Weichselbaum (1885) followed this up by demonstrating the same points in connexion with glanders in the human subject.

Distribution.—The glanders or malleus, as we now know it, has then long been recognised as a distinct disease affecting horses, especially when kept in close confinement or when herded in large numbers. It is met with most frequently and in its most characteristic forms in countries where horses have long been used. It is therefore specially prevalent in Europe, certain parts of Asia, and in North Africa; and as regards its general distribution, it is said to become much more prevalent, though in a milder form—southern glanders,—as we pass farther and farther south. The disease has been introduced from the regions above named into other countries, and is now met with in South Africa, Canada, the United States, and Argentina through the importation of affected horses. In Great Britain the number of cases of glanders detected has risen from 636 in 1874 to 2499 in 1903. Of the recorded cases London claims about 75 per cent, one half of the remainder occurring in the "Home Counties" of Middlesex, Kent, Essex, and Surrey. The large cities—Liverpool, Manchester, Birmingham, and Glasgow—supply the bulk of the remainder.

Etiology.—Infection usually takes place by direct contact or by inoculation of a cut or abraded surface with the purulent discharge, or with urine, saliva, or milk of a glandered animal that may have accumulated on mangers, nails, woodwork, harness, blankets, grooming tools, and so forth; or a similar inoculation may occur during an operation on, or a dissection of, such an animal. Farcy is found, therefore, in farmers, ostlers, stablemen and coachmen, cavalrymen, veterinary surgeons, tanners, and others who are brought into direct contact with glandered horses. Moreover, Babes found latent glanders in "horsy men" who had died from other diseases. It is interesting to note, however, that glanders or farcy amongst knackers is a comparatively rare disease; it is certainly met with far less frequently than one would expect. The disease is seldom transmitted to women, except when they have washed the clothing of infected patients, or, rarely, by coitus.

Babes performed a series of experiments to demonstrate that infection can be set up by glanders bacilli when mixed with lanolin or lard and rubbed into the healthy skin of guinea-pigs. It is supposed that the bacilli make their way into the various follicles, especially into those of the hairs, and that multiplying there they gradually make their way through the epithelium into the deeper tissues, whence they pass by the lymphatics and even by the blood-vessels to various parts of the body. Nocard arrived at a similar conclusion, and found that these bacilli were readily absorbed even from the intact mucous membranes, especially those of the eyelids, nostrils, larynx, or intestinal tract. Moreover, as has been pointed out by Nocard and by Sir J. M'Fadyean, infection by feeding

takes place probably fairly frequently among horses, cats, dogs, and menagerie animals; indeed, the balance of evidence seems to favour this as being the commonest method of natural infection, those who have the widest experience maintaining that the evidence in favour of infection by inhalation is far less convincing. The answer to the question whether the affection of the lungs is primary or secondary depends of course on the answer given to the question, Does the natural infection take place by the alimentary or respiratory tracts? Although the disease is spread principally by the discharges and by such excretions or secretions as urine and milk, diseased organs and tissue may also serve as vehicles for the spread of the disease. Prof. Sherrington and Bonome find that in acute cases in both man and animals the *Bacillus mallei* can pass through the kidneys into the urine, even when no lesion can be made out either with the naked eye or under the microscope. Bonome and others also maintain that the glanders bacillus passes from the parent to the fœtus in the case of the foal, the dog, and the guinea-pig, not only at those points at which placental hæmorrhages occur, but in some instances in which the structure of the placenta appears to remain intact. When the bacillus is found in the circulating blood, a condition usually occurring during a febrile attack or after the injection of mallein, the disease runs an exceedingly rapid course, and the patient succumbs with most acute symptoms. Under similar conditions the bacilli may be demonstrated in the bone-marrow.

The horse, then, may be looked upon as constituting the reservoir from which infective material may be continually supplied, just, as pointed out by Col. Bruce, as the wild cattle of South Africa form a reservoir for the tsetse-fly disease. The disease may remain latent for months, or even years, and Sir J. M'Fadyean contends that cases of occult glanders in place of constituting the exception are the rule. There can be no doubt that a case of declared glanders is a centre of infection, but it is probable that even occult cases are infective, though perhaps not so frequently. So numerous are outbreaks amongst horses and so rare are they in man (the Registrar-General reports an average of only 4·34 cases a year between 1886 and 1904; there were 8 in each of the years 1889 and 1903; 6 in each of the years 1887, 1893, and 1899; 1 only in 1896; and 4 in 1904) that we must conclude that if equine glanders were exterminated, farcy in the human subject would also disappear.

It must be borne in mind that, although the human subject usually contracts farcy from a glandered horse, the disease may be communicated from man to man, whilst he in turn may, as pointed out by Bollinger, become a centre from which an extensive epizootic may spread. Fortunately, man is not so susceptible to this disease as are the equidae; but although this is now fully recognised, it is equally well recognised that a chronic case in the human subject may give rise to an acute case in a horse, or even in another human being, as, for example, when the disease is contracted during an autopsy or surgical operation. Moreover, these chronic cases in the human subject may extend over

years, and, as during the whole of that time, with the exception of such periods when, from the temporary healing of the sores, the disease may be said to be latent, the patient needs constant nursing and dressing, he may be a continual source of danger to those in contact with him. During part of this infective period the patient may be engaged in his ordinary work, and may thus unwittingly spread the infection. In the human subject, as in the horse, the disease may be latent from the first, then suddenly becoming acute it is often not recognised, and so may constitute a very dangerous source and centre of infection. Dr. Nuttall and Mr. Strangeways mention several series of cases with peculiar modes of infection. Of two published by Rémy in 1897, one was "a woman who became infected whilst making horse-hair mattresses"; the second "a person who acquired glanders from being struck by the fist of a man who owned a glandered horse." Two cases were recorded by Grawleswki in 1893; a "washerwoman developed a glanders pustule three days after washing the clothes of a man who had died of the disease"; the other was "an old man who attended a person who died of glanders, and developed initial lesions in places where he was accustomed to scratch himself." A patient with a glanders lesion may inoculate himself at other points by scratching himself with his infected finger-nails; and it is stated that the infection "may occur in man through coitus." It is recorded that a woman carrying a breast-fed baby down the steps of a tenement situated near a stable passed the stable door as a led horse was being brought out; just at the moment the horse snorted and threw some of his foam on the child's face. The child acquired glanders; a sister who nursed it also contracted the disease, being infected by the child's nasal discharge which came in contact with her nipples. Both patients succumbed to the disease.

It has already been pointed out that the virus from a case of chronic glanders may produce an acute condition in a man or animal into which it has been inoculated. Speaking generally, it may be accepted that when a micro-organism is cultivated outside the animal body, it becomes more resistant and less virulent. It is well known, however, that by a process of "passage" of such a micro-organism through a succession of animals of the same species, it usually becomes, on the one hand, more virulent for that species, but, on the other hand, rapidly loses its virulence for certain non-allied species. Further, even in the same species the bacillus may find the conditions for its growth varying very markedly from time to time, corresponding variations in the manifestations of its presence being observed. The bacillary factors in the equation vary greatly from the outset, as the organism taken from an animal—the horse or the guinea-pig—may be modified by special methods of treatment. Under cultivation, and, according to Straus, after passage through a wolf, this virulence falls off very rapidly until the bacillus is little more than a saprophyte. If the parasitic properties are to be retained, it is essential that the bacillus should now and again be passed through a susceptible animal. Gamaleia, working with the Spermophilus, and Foth, using field-

mice, found that continued passage through these animals exalted the virulence of the bacillus in a most remarkable degree; whilst Sacharow, basing his experiments on the analogous experiments on rabbits with streptococci, found that the *B. mallei* passed through a series of cats became much more virulent for cats, but considerably less so for horses. Intracerebral inoculation into susceptible animals so raises the virulence of the *B. mallei* that it becomes lethal for dogs—animals usually singularly resistant to its attacks. As regards the second factor in the equation, although certain species are naturally much more susceptible than others, individuals of a species which normally has a fairly high resisting power may have that resistance broken down or interfered with by anything that interferes with the normal metabolism of the animal. Overwork, bad food, overcrowding, exposure, or disease, in fact anything that weakens the individual physically or constitutionally, renders him more susceptible to the attack of this bacillus. For example, it is recognised that the overcrowding of horses in the metropolitan stables is a most potent factor in the spread of glanders. Horses, each of which should be supplied with 15,000 cubic feet of air per hour, are only provided with one quarter, or even less, of that amount. In war time, overwork, bad food, and want of sleep play a similar part, whilst experimentally it has been shewn that small, comparatively insusceptible rodents, in which a phloridzin glycosuria is first produced, become much more susceptible to infection by glanders. A similar diminished resistance to this and certain other infective conditions has been noted in human patients suffering from the more severe forms of diabetes. In consequence of this great but varying resistance, and of the long periods during which the *B. mallei* can remain alive in the living animal, the so-called masked glanders of the horse and the chronic glanders of the human subject assume an importance that otherwise they would not possess. The resistance being broken down we may have a regular auto-infection and the outbreak of an acute form of the disease in a case in which, although the infection has been going on for some time, the disease was quite unsuspected. The number of those cases revealed by the mallein test is referred to elsewhere [*vide* p. 210].

Bacteriology.—If the pus or broken-down tissue from an actively growing glanders nodule be mixed with a little sterile saline solution, and a small portion of this be allowed to trickle over the cut surface of a sterile, slightly acid or neutral potato, which is then incubated at the temperature of the body, bright yellow or honey-coloured colonies soon make their appearance on the surface of the potato, and grow so luxuriantly that in eight or ten days the colonies of other organisms, if any, are overgrown, the growth going on more rapidly as the colonies become larger and run together. In these later stages the shining or glistening surface assumes first a peculiar fawn-brown, and ultimately a chocolate or *café-au-lait* colour. Blood-serum may be used instead of potato for the purpose of obtaining a primary growth. On this medium, kept at the temperature of the body, small isolated transparent colonies

are well seen in about 48 to 56 hours. Yolk of egg also forms an admirable culture medium, the growth appearing as small nodules or tubercles in about 24 hours. White of egg is not a good medium. The bacillus will grow in or on almost any of the ordinary cultivation media, especially when they are made slightly acid or neutral, and are kept at the temperature of the body (optimum temperature 36° to 37° C., minimum 21° C., maximum 42° C.; growth being inhibited at 43° C.). In gelatin it forms a whitish growth made up of chains and threads coiled irregularly and penetrating the gelatin in various directions, and ultimately brings about slow liquefaction. On agar-agar it forms a transparent greyish-yellow growth, which gradually deepens in colour. On glycerin agar-agar, on which it grows more luxuriantly when milk is added, it appears (even at the temperature of the room) as a broad, white, transparent shiny line, which follows the track of the needle. On a purée of potato, or in potato-gelatin or potato-agar, it forms prominent translucent plates, with a greyish periphery and a shining fawn-coloured central part. In bouillon containing glycerin it forms a cloudy growth, which after a time falls to the bottom of the tube in the form of a curious stringy deposit. It appears as a white growth, at the end of a couple of days, when seeded on sterilised carrot. Milk is coagulated in from 8 to 10 days when the culture is kept at 37° C. It is curious to note how the pigment differs on these various media, and according to the age of the growth. The growth may be white, as on gelatin, or it may be canary-yellow at first, later assuming a fawn colour, then an orange, and lastly a brown or chocolate colour. On potato there is often a greenish or greenish-blue discoloration in the immediate neighbourhood of the growth.

The bacillus when examined under the microscope is 1·5 to 3 or even 5 μ long by 0·25 to 0·4 μ broad, and has rounded ends. It may, however, assume club or branching forms; sometimes it grows in the form of threads 10 to 25 μ long, or it may assume a coccal form. No spores are seen in its substance, but sometimes its protoplasm is fragmented, or, at any rate, is very irregularly stained in deep and light bands and patches. It is said to be non-motile; but some observers maintain that, in certain conditions, the bacillus possesses the power of motion, especially when grown aerobically, the organism appearing to make its way to the free surface. Sir J. M'Fadyean points out that ordinary cover-glass preparations of farcy pus or material from glanders nodules containing glanders bacilli may be first stained with any of the ordinary basic aniline dyes—methylene blue, gentian violet, or fuchsin. Thionine blue is also a very useful stain. The nuclear detritus in these sections is then decolorised by means of a 4 per cent solution of acetic acid for about 5 to 10 seconds, the bacilli resisting the decolorising action of the acid.

Differential staining of the organism when in the tissues is not a very simple matter, as, although it takes the aniline dyes very greedily, it gives

them up very readily. Gram's method is no use for this purpose ; Noniewicz's method for staining the bacillus is to stain for two to five minutes in Löffler's methylene blue (concentrated alcoholic solution of methylene blue 30 c.c. ; caustic potash 0·01 per cent solution 100 c.c.), to wash in distilled water, and then decolorise for from 1 to 5 seconds, according to the thickness of the section, in a mixture of 75 parts of a 0·5 per cent solution of acetic acid and 25 parts of a 0·5 per cent watery solution of tropæolin ; to wash again in distilled water, and, after spreading the section on a slide, to dry it, first with blotting-paper, and then in the air or over a spirit flame. Clear by dropping xylol upon the section (oil of cloves, origanum, and aniline oils must be avoided), and mount in Canada balsam. The bacilli are stained dark blue or nearly black, and the tissue light blue. To obtain good differential staining in bacilli contained in sections Sir J. M'Fadyean uses the following modification of the tannic acid mordanting method, which appears to be greatly superior to any other method yet recommended. The tissues hardened in alcohol are embedded and cut in paraffin. Using exceedingly thin sections, the paraffin is removed and the sections are stained for half an hour in methylene blue either with Kühne's carbolised solution or Löffler's alkaline solution, or simply a 1 per cent solution in 10 per cent alcohol ; rinse in water and then transfer to a 4 per cent solution of acetic acid in water for a few seconds, then rinse in water ; "the acid solution almost entirely decolorises any normal tissue surrounding the lesion, and the latter is reduced to a pale blue"; then immerse the section for 15 minutes in a saturated aqueous solution of tannic acid, wash thoroughly and stain for 15 to 30 seconds in a 1 per cent aqueous solution of acid-fuchsin, wash in water, dehydrate, clear in cedar-wood oil, and mount in xylol-balsam. "In sections thus treated the nuclei and nuclear detritus in the lesion have almost entirely lost the blue stain, and the tissues are for the most part of a faint red, while the bacilli are of a light blue colour."

As it is sometimes exceedingly difficult to obtain cultures from nodules, it may be advisable, for diagnostic purposes, to use Straus's test (72). This observer inoculates a male guinea-pig or a field-mouse subcutaneously in the middle line of the abdomen, or intraperitoneally, with portions of the suspected material, and later, if necessary, obtains cultures of the bacilli on potato or blood-serum. After subcutaneous inoculation with the glanderous material from which the diagnosis is to be made, tumefaction appears at the seat of inoculation, the skin ulcerates, and a mass of soft, almost purulent material is discharged, a chronic ulcer, with a waxy looking base and dark-red irregular, indurated and raised margins, being left. From this issues a sero-purulent discharge. Around it there may be an eruption of vesicles and pustules, or even gangrene, occurring during the second week. In some cases the ulcer may heal; the lymphatic glands in the neighbourhood, however, become enlarged and tender, and may then ulcerate. The lymph-vessels become red and painful on pressure, the veins may become thrombosed, and at the end of two to four or five weeks the animal dies, with a general infection, the lungs and spleen then usually being involved. In the male the testicles are swollen, and later an acute inflammation causes considerable enlargement of the joints. Field-mice similarly inoculated

die in three or four days. Intraperitoneal injection into a male guinea-pig of the discharge from an ulcerated mucosa or gland sets up a much earlier inflammation of the testes; this often occurs as soon as the third or fourth day, and in the fluid between the two layers of the tunica vaginalis testis glanders bacilli may be easily demonstrated, either by microscopic examination or by the cultivation test. In these experimental cases the primary changes are inflammation of the lymphatics and orchitis; the nasal mucous membrane is not affected until the later stages of the disease. As this later test may occasionally fail, it is usually advisable to repeat the experiment on two or three guinea-pigs. Even when these succeed it is advisable to stain the bacilli by Gram's method in order to confirm the diagnosis by elimination. Pure cultures of the *Bacillus mallei* injected into horses, rabbits, and the animals already mentioned, produce characteristic glanders of the constitutional form. White mice and ordinary house-mice are more refractory, but they also may be infected by very virulent bacilli. Dr. Nuttall and Mr. Strangeways, collecting evidence from various sources, state that, in addition to the animals above mentioned, cats and hedgehogs are highly susceptible to the disease. Rabbits, the goat, sheep, camel, young dogs, and pigs (the latter not by subcutaneous injection) are more resistant, whilst adult dogs and pigs, cattle (old and young), the chicken, linnet, and frog all appear to be completely resistant. As already pointed out, the disease occurs spontaneously in the horse, mule, and donkey. In one menagerie I found two lions affected, probably infected by glandered horse-flesh; tigers, leopards, and bears are also said to contract the disease from this source, the bacilli gaining access to the tissues through wounds made by the spicules of bone broken during the chewing process. Some of the cases that appear to be set up by ingestion may be due to infection through such a channel. One case of direct infection in the human subject was traced to the use of an imperfectly sterilised hypodermic syringe with which cultures of the glanders bacillus had been injected. The specific bacillus may be associated with streptococci and the *Staphylococcus pyogenes aureus*; and it is probably this latter organism that gives rise to the peculiar phlegmonous lesions sometimes seen in the course of an attack of glanders.

The glanders bacilli if kept moist may remain alive for a month. Bonome says that when dried (kept at a temperature of 25° C.) they die within ten days, but if allowed to remain moist they may be alive and virulent at the end of twenty days; they are said to remain alive for fifteen or twenty days in ordinary potable water. According to Löffler they always succumb within four months. Sanarelli maintains that the bacilli resist putrefaction for a period of from fourteen to thirty days. Again, it is stated that in aerobic cultivations they die in a few days, but that they may survive for two months, provided the cultures are anaerobic. They may certainly remain alive when grown on culture media for about a month. These organisms are readily affected by extremes of temperature and by even weak antiseptics. If kept at

15-16° C. they die in about five days. It is said that at a temperature of about 55° C. they succumb in ten minutes, and at 62° C. they die in one minute, though Bonome says that he has found them still alive after an exposure for six hours to a temperature of 70° C. At 75° C. they are killed in five or six minutes, and at 90° C. to 100° C. in three minutes. Bromberg states, however, that in an old cultivation all the bacilli are not killed after exposure to a temperature of 100° C. for as long as half an hour. Exposure to direct sunlight for a day ensures the death of the bacillus. The action of even weak antiseptics on these organisms is very marked. They are rendered inert and incapable of growth by 1 : 2000 perchloride of mercury solution (1 : 100 kills them in fifteen minutes), or 1 : 100 turpentine in water. Watery solution of carbolic acid, 1 : 20, has a similar effect in five minutes, or 1 : 100 in two to four hours.

It has already been stated that the glanders bacillus when cultivated as a saprophyte loses its virulence very rapidly, and in certain conditions it so far loses its activity as to set up an exceedingly modified form of the disease in the horse; for, although it is recorded, *pace* Löffler, that an unoccupied stable has remained infected for a period of a year and a half, most observers point out that if the organism exists outside the tissues for any long period it becomes greatly attenuated. Although the *Bacillus mallei* grows best in the presence of oxygen, it is capable of growing anaerobically; indeed, when so grown it appears to have a greater power of forming toxins than when it has access to a free supply of oxygen. It has also been stated that the virus may be exalted by passing it through a series of cats, under which conditions it ultimately becomes less virulent for the horse; a horse inoculated with virus so attenuated passes through a modified attack of the disease, and is then proof against attacks of more virulent cultures of the organism. This observation still requires corroboration.

Mallein.—Babes, Kalning, Preusse, and Helman prepared from the *Bacillus mallei* a substance similar to that prepared by Koch from the *Bacillus tuberculosis*. An active toxin-forming glanders bacillus (which may be obtained by smearing the pus from a freshly-opened farcy lesion of a horse over the cut surface of a sterilised potato, the discrete colonies being selected as seed material) is cultivated in peptone bouillon to which a small proportion of glycerin has been added. The culture, if pure (tested from time to time by inoculating potatoes), is incubated at a temperature of 37° C. for a month or six weeks; it is then placed in the autoclave and heated to 120° C. for twenty minutes or half an hour on each of three successive days to destroy all the bacilli. To prevent putrefaction, carbolic acid in the proportion of 0·5 per cent is added, after which the fluid is filtered through a porcelain filter in order to remove the bodies of the bacilli. This fluid contains the active toxic material, secreted by the glanders bacillus, in such quantities that when injected in definite doses (1 c.c.) it gives rise to a very distinct reaction in an average-sized glandered horse, whilst in horses unaffected with

glanders no reaction is provoked by a dose of even 6 c.c. In Roux's method of preparing mallein the sterilised filtrate is concentrated by evaporation until it becomes a syrupy fluid. This is then diluted with ten times its volume of 0·5 per cent solution of carbolic acid. Of this carbolised fluid, which "keeps" well, 3 c.c. is sufficient to set up a definite "reaction" in a glandered horse. The term mallein is sometimes retained for a watery or watery glycerin "extract" of a potato cultivation of the *Bacillus mallei*. It is stated that this may be used as a diagnostic agent, but that it has no curative effect. To the bouillon filtered cultivation described above the term Morvin has been applied by Motoe and A. Babes, who ascribe to it not only a diagnostic but a curative value. It is quite possible that the very different values ascribed to mallein as a diagnostic agent by various observers may result from the use of these different reagents. Mallein has been recommended for diagnostic purposes in the human subject, but there appear to be clear indications against its use. In some of the chronic cases in which it has been used no reaction has been obtained, while in others, although no vascular reaction, such as takes place when tuberculin is injected in tuberculous cases, occurs, there may be general reaction, marked by a rise of temperature of 2° or 3° C., pain in the head, and faintness, all during the first twelve to eighteen hours. This is followed by pain and swelling at the seat of injection, which may last for two or three days. Since a dose of mallein sufficient to give a diagnostic reaction may cause a chronic case to assume an acute character, it is evident that this reagent must be used with the utmost caution. Even in suspected acute cases it is doubtful whether we are justified in using mallein with the object of determining the nature of the disease. As regards the dose, it is maintained that $\frac{1}{10}$th or even $\frac{1}{30}$th of the dose that will set up a reaction in the horse and is innocuous to that animal will give a reaction in the human subject. Whether Sir Almroth Wright's opsonin method will be helpful in either the diagnosis of this disease or in the observation of its course during treatment still remains to be proved. As there is some misconception as to the nature of the reaction to mallein, it may be stated generally that unless the temperature rise 2° C. rapidly, commencing six to eight hours after injection, and goes above 40° C. (this is often repeated twenty-four hours later), and a swelling of three or four inches in diameter and one to one-and-a-half inch in height appears, and continues to increase for a number of hours, after the sixteenth or eighteenth hour, the reaction is not characteristic. It should also be borne in mind, as Nocard points out, that this reaction can be obtained only when the temperature is normal; mallein, therefore, should never be injected for diagnostic purposes when the temperature is already high. Should no specific reaction be obtained, a second injection may safely be given eight or ten days later. Babes recommends, therefore, in all outbreaks of glanders that after destroying all the animals that are manifestly glandered, the "contact" animals should receive a couple of injections of mallein at intervals of one to two weeks. All the horses that have reacted typically should be isolated at once. Remove all the

animals that do not react. Keep those that have reacted once in thoroughly disinfected stables, and inject with small and increasing doses of mallein, keeping them quite apart from other animals, providing separate drinking-vessels, etc. Test with a diagnostic dose every two months, and be guided by reaction and clinical course of the disease as to whether the animal should be slaughtered. If it continues to react, or if the glanders becomes manifest, there should be no hesitation about this.

Glanders

Morbid Anatomy.—In horses that come into the hands of the knacker or into the post-mortem room the lungs are almost invariably involved, though other lesions are fairly frequently met with. The best description of the typical pulmonary lesions of glanders is that given by Sir J. M'Fadyean, on whose description the following account is based:[1]—On passing the hand over the surface of a lung affected with glanders, firm, hard nodules may be felt not only immediately under the pleura, but also, on deeper palpation, at some distance from the surface. On section, pearly grey nodules, some with a peculiar yellowish-white centre and surrounded by a dark, hæmorrhage-like zone, may be seen; these vary in size from points just visible to the naked eye to nodules the size of a pea, a hazel-nut, or even a walnut—the pea-sized nodules being the most abundant. I have seen a glandered lung in which only a couple of these nodules could be made out; whilst in others I have seen from a dozen up to several hundreds. These nodules, however, can never be spoken of as innumerable; so that in this respect they differ from true pulmonary tubercles, which, in the horse, if not innumerable, can be counted by thousands. Sometimes dark hæmorrhagic areas may be noticed in the lung, in which, scattered at intervals, are grey nodules similar to those described above. Within a greyish capsule is a white centre which may be somewhat softened; though it seldom undergoes purulent degeneration. When the centre is firm it may often be "easily shelled out with the point of a scalpel from the greyish peripheral portion"; in some cases this central portion undergoes calcareous infiltration. On examining the hæmorrhage-like areas under the microscope, it is found that the central zone consists of lung-tissue densely packed with polymorphonuclear leucocytes or pus-corpuscles, which occupy the alveoli and compress the septa; in this region there is little or no proliferation of the epithelial cells lining the alveoli. Immediately around this area is a zone in which may be seen numerous epithelioid cells, each containing a single vesicular nucleus, which does not stain nearly so deeply as does the polymorphonuclear form; here also a few giant-cells may be found among the epithelioid cells. Except at the margin of this zone, it is difficult to make out the remains of the walls of the air-vesicles; but immediately outside this is

[1] Through the kindness of Sir J. M'Fadyean I have been enabled to make an examination of these lesions of the lung, and also of other tissues.

a third zone in which, from thickening of their walls, the air-vesicles are considerably smaller than normal. The thickened septa are composed of fibrous tissue with elongated nuclei; whilst the cavity or vesicle contains a lining of more or less cubical epithelial cells, a number of free epithelioid cells, a few leucocytes, and large mononuclear cells containing particles of carbon. Here too may be seen a few strands of coagulated fibrin. Surrounding this area is a zone in which the changes are indistinguishable from those found in croupous pneumonia; the inter-alveolar capillaries are distended with blood, and the alveoli contain delicate coagula in which leucocytes, detached epithelial cells, and a few red blood-corpuscles are entangled in a network of coagulated fibrin. It appears that this pneumonic condition is the first indication to the naked eye of the presence of a glanders nodule; although by careful microscopic examination we learn that the small area of infiltrated leucocytes constitutes the primary change. This small area becomes surrounded by a pneumonic zone, in which thickening of the alveolar walls and packing of the alveoli with various kinds of cells may be observed; the process spreads from the centre outwards, the pneumonic zone indicating the part most recently affected. When the process is more chronic this so-called hæmorrhagic appearance is absent, and the centre of the nodule, as it softens, is found to be composed of leucocytes and granular detritus; outside this is a zone in which large epithelioid cells are abundant, and amongst them a few giant-cells which are indistinguishable from those met with in a tuberculous nodule. The pearl-grey capsule, as in tuberculosis, is made up of connective tissue in various stages of development, whilst immediately outside this is a zone which consists of fibrotic lung tissue, in which the walls of the alveoli are enormously thickened; the air-vesicles are correspondingly diminished in size, and are lined by distinctly cubical epithelium: this part of the lung-tissue closely resembles the white pneumonia described by Virchow in the lungs of syphilitic children, a condition also found in other forms of interstitial pneumonia occurring in the adult. As in these conditions, there is in glanders considerable injection of the vessels in this new tissue; and there may be fibrinous exudation into the air-vesicles just beyond the area of the healthy lung. Then, too, as in tuberculosis, a central area may shrink and become calcified; and this area, surrounded by a distinct fibrous capsule, represents the nearest approach to healing and isolation that ever occurs in the case of a glanders nodule. Sir J. M'Fadyean believes that in the horse the nodules originate in connexion with the air-vesicles, but whether in consequence of the arrest of glanders bacilli in an alveolar capillary, or of the penetration of the bacilli into a vesicle with the respired air, he does not decide; he inclines, however, to the belief that, as the nodules are comparatively few in number, and are often confined to one lung, the infection is not spread by the blood; moreover, the irregular distribution and the difference of age of the nodules point rather to a dissemination of the bacilli by the air-passages. If the starting-point of the nodule be the multiplication of

bacilli that have come to rest in the cavity of an air-vesicle, infective matter may find its way from this point along the bronchi to other portions of the lung, to form fresh foci of disease. In support of this opinion it may be urged that the small bronchi often contain numerous leucocytes, some in various stages of degeneration; whilst evidence of proliferation in the perivascular lymphatics is comparatively rare. In certain cases, indeed, the lymphatic system seems to be more directly invaded; but such invasion appears to go on much more slowly and in a much more localised fashion than in the case of tuberculosis; the lymphatic glands are seldom enlarged, and, in marked contradistinction to the glands in tuberculosis, they present remarkably few changes of any kind, especially when examined merely with the naked eye. In consequence, however, of the lymphatic infection large areas of the lung-tissue may be more or less consolidated; the interlobular septa are thickened and fibrous-looking, whilst between these there is evidently a pneumonic exudation from which a little clear fluid may escape. This mass of lung-tissue is usually moist and of a pinkish colour, and here and there in it small white points may be distinguished. These points, when examined under the microscope, are found to consist of a group of air-cells, crowded with leucocytes surrounded by a number of epithelioid cells; whilst the pink, consolidated, moist mass consists simply of lung-tissue in a state of croupous pneumonia, in which the lymphatics of the thickened interlobular septa are found to contain an exudation similar to that present in the air-vesicles. In certain cases the solidified portion of the lung, usually the lower edge, is more like the white pneumonic lung of Virchow. In this consolidated mass we find a condition of chronic bronchitis and peribronchitis, the whole bronchial wall being apparently replaced by granulation-tissue consisting of round cells and young connective tissue; whilst in the lung near or around this mass we have a condition of chronic interstitial pneumonia. This is usually associated with the presence of nodules of glanders in other parts of the lungs. When the nodules are close to the surface of the lung the overlying pleura is always thickened, especially in its deeper layer, where the thickening is often the result of irritation of the lymphatics, resulting in the formation of fibrous tissue; it is sometimes associated also with the development of villous fibrous granulations on the pleural surface. Although these glanders nodules occur most frequently in the lung, similar nodules may be found in the lymphatic glands, or liver. They have an opaque, evidently degenerated centre surrounded by a capsule of well-developed translucent fibrous tissue, or the whole nodule may be grey and translucent, affording evidence of a reaction of the connective-tissue cells, and of a tendency to recovery. In some instances the central portion of the nodule, instead of becoming caseous, may soften, and in course of time "burst spontaneously and discharge pus" (M'Fadyean). It is now generally accepted, states the same author, that all the more rapidly formed nodules in acute cases are composed primarily of aggregated polymorphonuclear leucocytes which

appear to migrate from congested vessels (chemiotaxis, the result of the attraction of the glanders poison), and then, under the influence of the glanders bacilli, to undergo a rapid necrosis (the chromatotaxis of Unna). There is little reaction of the connective tissue, the disease runs a rapid course and ends fatally. In this special form of necrosis the nuclei of the cells, especially those "in the centre of a nodule, become disorganised while the cell-body is still intact, and the fragments of chromatin, resulting from the nuclear disintegration, for a considerable period retain a strong affinity for the ordinary nuclear stains. . . . This peculiar degeneration sets in almost immediately, and the nuclear fragments are remarkably persistent, since they are found in nodules whose fibrous capsules indicate that they are of old standing. I have been most struck," he continues, "with the importance of this form of necrosis as an assistance in the recognition of glanders lesions by observing that it occurs not only in the ordinary circumscribed nodular lesions, but is also a marked feature in acute diffuse glanderous pleurisy. In such cases the layer of fibrinous lymph on the surface of the inflamed pleura contains numerous polymorphonuclear leucocytes, which are here and there aggregated into clusters like miliary abscesses. Similar collections of these cells are met with in the same position in the much commoner cases of streptococcus pleurisy in the horse, but the two lesions are readily distinguishable, histologically, by the fact that pronounced chromatotaxis of the leucocytes occurs in the glanderous pleurisy, while it is entirely absent in the other."

In most of the acute cases this mass of degenerated leucocytes is surrounded by a zone of tissue in which the lymph-spaces—or, as we have seen in the lung, the alveoli—are filled with fibrin. As the process becomes more chronic, *i.e.* when the fixed tissue-cells have had time to react to the stimulation set up by the glanders bacilli and their products, and, possibly, also by the degenerated tissues and fibrin (which now may be looked upon as playing the part of foreign bodies), we find at the periphery of the nodule, in the region where the tissues though not destroyed are somewhat damaged, a marked proliferation of the fixed connective-tissue cells, later the formation of fibrillated tissue from these multiplying cells, and finally a well-developed fibrous capsule to the nodule. This constitutes the translucent zone found surrounding the more opaque centres in so many of the chronic glanders nodules in the lung. Sir J. M'Fadyean considers that "the peculiar degeneration (chromatotaxis) which never fails to set in in the central part of a glanders nodule" and "the slight tendency to peripheral extension which the glanders nodule ordinarily exhibits" are two features by the aid of which the glanders nodule may infallibly be distinguished from the ordinary miliary abscess. Where the process is more acute this localisation may not take place; the area of degeneration extends, the centre undergoes marked and rapid "puriform" softening, there is no cell-reaction on the part of the connective tissue, and the limiting fibrous tissue zone never makes its appearance.

It is evident that glanders must be looked upon as the local and outward manifestation, or as the group of primary phenomena of a peculiar pyæmic condition which may be spoken of as farcy; indeed, one writer (Bendall) says that as the malignant pustule of charbon in man is to the constitutional blood-poisoning of anthrax, so the local glanderous affection of the nose is to the general pyæmia of farcy.

Symptoms.—In many cases of glanders there are absolutely no symptoms on which a trustworthy diagnosis can be based, and it is only since the use of mallein has come to be properly understood that any accurate estimate of the number of glandered horses in the stables of our large towns has been possible (for every manifestly glandered horse found, Sir J. M'Fadyean calculates that at least five will react to the mallein test). The earlier descriptions of the symptoms have almost invariably been taken from ordinary cases of advanced glanders, and are now therefore of comparatively little value except from an historical point of view. The earliest symptom in the horse is usually an unaccountable *loss of condition.* Though apparently under exactly the same conditions as regards food and appetite, general hygiene, exercise, and work, the animal falls off in general health. This falling off is often accompanied by more or less polyuria, and is generally followed by swelling of one or other of the limbs, usually of the hind leg, in which there is found a kind of inflammation of the lymphatic system—*glanderous lymphangitis*; "farcy-buds" and "swollen leg" often being marked features of the disease at this stage.

Following or accompanying these symptoms, *submaxillary enlargement and induration* afford still more positive evidence of the presence of the glanderous condition; and a short dry cough, indicating the presence of some lesion in the lungs, is often met with, sometimes before any other symptom has had time to manifest itself. The frequent occurrence of this cough is readily understood when it is borne in mind that in both farcy and glanders the lungs are so frequently involved that it is held that in every case a lung lesion may be found if a careful enough search be made. It is sometimes stated that a thin, watery discharge, which gradually becomes thick, viscid and glue-like, sero-purulent, bloody, and often extremely offensive, is pathognomonic of this disease, and that it should always be looked for. When present, such discharge may help us to form a correct diagnosis; but it has been abundantly proved that no great reliance can be placed on this feature, as it is only found in those cases in which nasal ulceration has made its appearance,—an ulceration which occurs in a very small proportion of the cases that come up for examination, and in these in the later stages only of the disease. On examining an advanced case of glanders the mucous membrane of the nose, especially that on the *septum nasi,* is found greatly congested in certain areas; in some cases, however, it presents a dull leaden colour. On the septum nasi, which should always be examined, small shotty nodules, usually surrounded by a congested zone, may be seen in the early stages of the disease; after a time these nodules become pale in

the centre, soften, and ulcerate, the softened central portion escaping and leaving a small, deep, circular ulcer with a sharply defined edge, as though the ulcer had been punched out. As these ulcers increase in number and size they gradually run together, and form serpiginous ulcers, which once recognised cannot easily be mistaken for anything else. When these ulcers heal, as they sometimes do, peculiar elongated or radiating cicatrices are left. The whole of the ulceration on the septum is not, however, of this character. In some specimens preserved at the Royal Veterinary College in Camden Town there is, as pointed out to me by Sir J. M'Fadyean, a kind of superficial erosion; beneath these eroded surfaces there appears to be very little infiltration, and it may be that this superficial ulceration or erosion is due to the action of the irritant or caustic discharge from some of the punched-out ulcers on the surface of the mucous membrane over which it flows. The two conditions are perfectly distinct, though the second form is not usually noted. With the ulceration there is often swelling of the nasal mucous membrane, with consequent obstruction of the respiratory passages and a peculiar "choking" breathing. At this stage marked submaxillary lymphadenitis is often present. The glands, usually swollen and indurated, seem little disposed to undergo suppurative changes. The disease may spread to the frontal sinuses; the skin on the forehead becomes thickened and tender; the subcutaneous lymphatics in the face and neck usually enlarge, and when opened are frequently found to contain soft, greasy, pyoid material. The swollen lymphatics are the so-called *farcy-pipes.* Along their course nodular dilatations may usually be seen; these are said to occupy the sites behind the valves of the lymphatics. In "*button-farcy,*" moreover, small tubercular nodules are met with in the skin of the limbs, or more rarely of the abdomen and thorax. In these positions also the so-called "worms" are often seen. The limbs (especially the thighs of both hind limbs), usually affected at an early stage, are stiff, hot, and tender; abscesses form, sometimes subcutaneously, at other times apparently in the substance of the muscles. The matter from a newly-opened farcy-bud has, as a rule, very distinctive characters; it is glairy or oily, and contains but a small number of leucocytes, so that usually it is easily distinguishable from staphylococcus pus, and "strangles pus." A most important point is that glanders bacilli are usually not very abundant in farcy pus; on the other hand, other organisms, such as staphylococci and streptococci, are seldom if ever present. It follows, therefore—and this is the result of general experience—that if, on microscopical examination, no bacteria can be found in the matter from a comparatively superficial lesion, such lesion is probably glanderous in its nature; and in such matter cultivation or inoculation experiments usually demonstrate the presence of the *Bacillus mallei*, even when present in very small numbers. The appetite, at first good, gradually becomes impaired; the animal loses strength and flesh; the cough gets worse; the abdomen is retracted; the coat, staring at first, gradually falls off, and the animal dies of exhaustion.

Farcy

Farcy is seldom a primary disease in the horse, but it appears to be the usual form of the disease in the human subject, in whom it assumes a form similar to glanders experimentally produced. In experimental glanders the malady usually appears as an acute or generalised pyæmic state, and the discharge from the nose and other nasal conditions make their appearance in the later and more chronic stages of the disease.

Morbid Anatomy. — These later stages are usually characterised by the presence of minute nodular new growths, very similar in structure to those described in the lung of the horse; they are made up of migrated leucocytes, which are very apt to undergo disintegration, especially in the centre, and thus to give rise to minute abscesses and ulcers. These nodules are found most frequently in the skin and subcutaneous tissue, in the mucous membranes of the organs of respiration, and, though less frequently, in the internal organs. In acute cases the ulcers, which as a rule are exceedingly foul, seldom heal; but in cases of chronic glanders, healing, partial or complete, often occurs. Farcy in man has been well described as taking the form of an acute or, more rarely, a chronic specific pyæmia, characterised by eruptions on the skin, on the nasal mucous membrane, or on both, frequently accompanied by the formation of intramuscular abscesses, sometimes of enormous size. The glands are rarely specially affected; there is usually inflammatory œdema and swelling of the limbs.

Pus is often found in the internal organs; in the kidney, between the stomach and spleen, in the posterior lobes of the brain, in the shafts of the bones, and separating cartilage from bone. In acute cases small abscesses, similar to those in the lung, are also found in the skin and mucous membrane. In the human subject a metastatic lobular pneumonia, almost identical with that met with in the horse, is often observed: it is, however, more acute, there is often intense congestion around the pneumonic area, and the centre of this area undergoes marked softening. In or around this pneumonic area the arterioles and capillaries may contain fat or oily emboli (Bendall), a condition supposed to be due to the absorption of fat from the rapidly degenerating or fatty necrotic tissue of the nodules. As might be expected, extravasations of blood from the obstructed capillaries often take place into the surrounding tissues. In acute glanders in man abscesses in the bone-marrow have been described. Bronchitis is comparatively common in acute cases, especially when the lung is affected: there is marked catarrh of the epithelial cells covering the mucous membrane, whilst the epithelial cells of the muciparous glands may disappear altogether. The pustules and nodules, both in the nasal mucous membrane and in the skin, appear to have a similar structure and course to those nodules met with in the internal organs; these have been summed up thus: (i.) an accumulation of cells, which (ii.) rapidly undergo degenerative changes; (iii.) congestion

of the surrounding vessels; (iv.) ulceration of the degenerated tissue, which is usually preceded by (v.) proliferation of the epithelial covering of the papillæ. The ulcers, as already mentioned, usually occur in groups and, gradually coalescing, form a serpiginous ulcer, often of considerable size. The extravasations of blood, so frequently met with in this condition, come from the distended vessels.

Symptoms.—*The period of incubation* after inoculation may be very short, 3 to 5 days, in which case the patient succumbs rapidly in 8 to 18 days; or it may be prolonged to one or two weeks or even more, and the patient may survive 21 to 42 days.

The more acute forms of glanders or farcy in man—the acute and subacute—are very difficult to diagnose, especially if there be no history to guide the physician. The disease is characterised by malaise, nausea, cerebral headache, vomiting, pains and tenderness in the epigastrium and hypochondrium, shivering and chills, which, however, may not and perhaps usually do not make their appearance until the later stages of the disease, when ulcers and abscesses have formed. There is usually some fever, but this may be absent. The rise of temperature is permanent, intermittent, or remittent. The thermometer may register 102° to 105° F., remaining at the higher limit for fourteen days. The pulse is full and respirations are rapid. Again, there may be ill-defined pain in the muscles and joints of the back and limbs, and the disease may simulate acute rheumatism, all these symptoms appearing within twenty-four hours. The patient may fall into an asthenic condition, and then into a "typhoid" state, and become deaf, dull, semi-comatose, and finally into a muttering delirium, coma, or complete unconsciousness. In such cases the disease may be mistaken for malaria or for pyæmia. There is often intense nervousness and irritability in these cases. Marked gastro-intestinal disturbance is often a prominent feature. Anorexia and nausea are commonly accompanied by constipation, followed perhaps by very offensive diarrhœa. There is usually excessive thirst, and the secretions are scanty. The gums become inflamed and small pustules or hæmorrhagic ulcers appear on them and on the hard palate. The fauces are dry and red or almost black; the tongue, of the same colour, is usually thickly coated, whilst on its posterior aspect small ulcers may be seen. The tonsils, the submaxillary, sublingual, and parotid glands, with their associated lymphatic glands, are often swollen and inflamed. There may be marked congestion of the larynx, sometimes associated with the characteristic pustules and superficial ulcers in this position, and with marked hoarseness and aphonia, often due to infiltration of the vocal cords. Abundant watery or viscid nasal discharge is commonly present in the early stages of the disease, later it may become purulent, hæmorrhagic, and offensive; ulceration, though present in acute cases, is not so frequent in man as in the horse. The nose is often swollen at the base and over the bridge, and is hyperæmic and hypersensitive; dried crusts of mucus mixed with pus and blood may accumulate in the nose and give rise to marked obstruction. Small and superficial red and purulent variolous-looking pustules, which

discharge a fetid serous or sero-sanguineous fluid, are often accompanied or followed by ulcerations of the mucous membrane of the nostrils, and of the cartilage of the septum, which, together with the vomer, may be perforated.

Farcy may be distinguished from ordinary pyæmia by the presence of these various skin eruptions. The more common of these are small circumscribed erysipelatous patches, which simulate very closely erythema nodosum. These patches often become the seat of pustules or of phlyctenæ, whilst in some cases gangrene of the skin supervenes. Bullæ of various sizes, containing a sero-purulent fluid, are also often met with: when they burst a raw surface is left, or if they dry up a hard crust, often mixed with blood, remains to mark the seat of the bulla. A pustular rash, similar to that found on the mucous membrane, and somewhat like that of small-pox, but without umbilicated pustules, is also often met with. The pustules, which commence as small red spots, are somewhat irregular in shape and size; they are placed on an inflamed base, and they may be surrounded by a white wheal-like ring. These do not dry, but form small ulcers which run together to form larger sores. In some cases marked œdematous swelling, similar to that observed around the abscess in other parts of the body, surrounds the furuncles, especially those situated on the face. This pustular rash is of very grave significance, as when it once makes its appearance recovery seldom if ever takes place.

Circumscribed swellings and multiple metastatic symmetrical (embolic) abscesses affect the subcutaneous tissue, the muscles, sheaths of tendons, fasciæ, bones—especially of the skull—causing necroses or softening of their substance, and joints, which may be distended with fluid. These abscesses are the one constant feature of the disease. They form rapidly—within forty-eight hours—the tissues around them are soft, sodden, and phlegmonous, and break down readily. At first they are hard, they then soften, and the patient has all the symptoms of pyæmia. They often point beneath bullous pustular patches or are covered by intensely inflamed skin. On pointing and bursting, or being incised, the inner surface of the wall is found to be very ragged, and huge foul ulcers or sinuses are formed, which have a rough granular edge and base, or walls, but no pyogenetic membrane, so that the pus often infiltrates the intermuscular tissue and sometimes makes its way into the joints. The matter discharged has a dirty grumous, darkish-brown, purulent appearance; or it may contain blood, sloughs, débris, and pus-cells, and, according to Dr. Bendall, a considerable quantity of free oil. There is usually swelling and redness of the lymphatics—lymphangitis—especially near a wound or bruise which has become infected, but general lymphatic infection is not so common as in the horse. The swellings found on the forehead, arm, and leg vary in size, being from one to three inches in diameter. The smaller swellings are often nodular; the larger ones fluctuate at an early stage. It must be remembered that glanders is often complicated by various coccal infections and other pyæmic processes. A

toxic albuminuria is found, and the urine is loaded with albumin; sometimes the urine gives the diazo reaction. Intense prostration supervenes, there is great emaciation, the heart is weak and often dilated, and there are signs of circulatory failure. The temperature falls, congestion of the lungs and sometimes pleuro-pneumonia sets in, the respiration becomes weak and laboured, and the patient succumbs in a state of extreme exhaustion. Acute farcy is an exceedingly fatal disease, only some 4 to 8 per cent of the patients recovering—death, as we have seen, taking place in from one to three weeks.

The diagnosis *of chronic glanders and of farcy in the human subject*, apart from the history of the case, is equally a matter of extreme difficulty, especially in the early stages of the disease, when there is no evident point of entrance, or when the wound has healed or the infection has taken place through an old wound. There is no initial stage, the incubation-period being said to terminate with the manifestation of acute symptoms. Its presence is not ushered in by rigors, though fever is a much more prominent feature in man than in the horse, and the course it runs is very variable, sometimes extending over a period of years. It may be stated generally, however, that all cases that extend beyond forty-two days, and have an incubation-period of more than ten days, are to be looked upon as being chronic. The first thing noticed may be a roseolous rash, which, disappearing, may be followed by a crop of papules or pustules, or, again, there may be a kind of erysipelatous redness, often very ill-defined, but fairly constant, extending over the whole face, followed by subcutaneous, periosteal, and intramuscular abscesses which never remain stationary; these may spread, sometimes rapidly, but later they have a marked tendency to heal. Such abscesses, which are often found in the skin and subcutaneous tissue of the forehead and eyelids, and in and around joints, seldom on other serous surfaces (Tedeschi records a case of chronic osteo-myelitis due to *Bacillus mallei*, which was followed by fatal glanderous meningitis, apparently the result of bacterial emboli, simple or mixed), contain yellow viscid or oily pus, especially when they are deeply situated, and discharge on the surface by sinuses. The granulation-tissue is very flabby and unhealthy, and the fluid discharged is sero-sanguineous, containing a number of leucocytes. When the abscesses are opened aseptically a few bacilli may be demonstrated. It is interesting to note that these phenomena usually manifest themselves on the fingers, limbs, and face, seldom on the nasal, buccal, or conjunctival mucous membranes or in the lungs, as primary lesions in the chronic form of the disease. Indeed, abundant nasal discharge, ulcer formation, which occurs in about 50 per cent of the cases with septal and palatal perforation, and affection of the lungs must be looked upon as evidence of an acute process or as secondary phenomena which usually only make their appearance shortly before the death of the patient. Similarly the lymphatic glands and the testes are not usually affected in man, but a leucocytosis often makes its appearance in these chronic cases. One of the most striking features in such cases is the alternation of the

destructive and the healing processes. Abscesses may appear to heal, only to break out again after an interval of months, invasion and arrest of the disease processes following one another at irregular intervals. One case is recorded in which the disease was chronic for three years, it then became latent for three years, and finally became acute and killed the patient. When the healing process is long retarded, thedischarges, especially when nasal or buccal, may become extremely offensive. In certain cases there may be marked congestion or even ulceration of the larynx or trachea, accompanied by œdema of the glottis, giving rise to a peculiar hoarseness or huskiness and coughing. Pulmonary complications are comparatively rare in chronic farcy.

Babes describes a condition in man, which corresponds to the masked or latent glanders in the horse, in which encapsuled nodules are found, especially in the lungs; such cases can only be diagnosed during life by the use of mallein. In one case, a groom who died from chronic nephritis, nodules were present in various parts of the body; from these nodules cultures of the *Bacillus mallei* were obtained. Another series of cases is mentioned, usually in coachmen, grooms, or men working amongst horses, in whom death was apparently due to intercurrent diseases; in them, after death, have been found nodules identical with those found in latent glanders of the equine species: these cases are supposed to be cured or in a fair way to recover. The lesion invariably consists of a nodule or mass of hard sclerotic tissue with a calcified centre; these nodules are found studding the lungs, and are usually accompanied by pleural adhesions of old standing. They may also be found in the mediastinal and bronchial glands, and in the spleen and liver. The lesions in one of these cases of mixed glanders took the form of chronic ulceration of the leg, which first healed, then broke out again, and after a time was followed by high fever, local gangrene, and the formation of an abscess in the cellular tissues of the leg. In this case the organisms present were found to be *Staphylococcus pyogenes aureus* and the *Bacillus mallei*; from which Babes concludes that the attenuated glanders bacilli may give rise to the formation of chronic nodules, which do not become acute until certain pyogenetic organisms gain access to them. These mixed infections, however, are of comparatively rare occurrence, and few observers have been able to corroborate Babes on this point.

A rise of temperature, various forms of skin eruptions, especially when they undergo rapid change of type, new crops of lesions appearing at intervals with partial or complete healing, are very characteristic symptoms of this prolonged condition. In chronic farcy the fatality is comparatively low. According to some observers over 60 per cent of the cases recover, the disease usually running its course in about four months, though there are many exceptions to this rule.

Syphilis and tuberculosis are the two diseases with which chronic glanders may be most easily confounded, but even when they have been eliminated the diagnosis is often a matter of great difficulty, and in many cases can only be made by a careful use of cultivation methods and of

Straus's method of inoculation of male guinea-pigs (see p. 208). Sir J. M'Fadyean points out that in the case of glanders, of the horse at any rate, the agglutination test may be utilised, agglutination of a culture of the *Bacillus mallei* being brought about by $\frac{1}{1000}$ dilution of the serum of an untreated glandered horse, but only with a dilution of $\frac{1}{200}$ of the serum of a normal horse. The pathogenicity of the bacilli should be tested on several animals—and should never be settled by one or two tests—as bacilli of extreme virulence may sometimes be isolated from material taken from cases in which local healing is apparently going on. This chronic form very often ends in the acute form, coma, and general collapse; indeed at one time this was said to be the invariable termination, but since the introduction of mallein as a diagnostic agent it has been found that cases of chronic or "latent" glanders may recover; this probably occurs much more frequently than was at one time supposed, as large a proportion as 50 per cent being said to recover. It is well to bear in mind that the slow development of the disease rather than the number and extent of the lesions is what we must look to as affording indication of a favourable prognosis. Slow healing of most of the sores, with now and again a more rapid closing of a single sore, may also be looked upon as being a sign that the disease may take a favourable turn and end in recovery.

As already noted, the diseases that are most frequently mistaken for chronic glanders are tuberculosis and syphilis. To distinguish tuberculosis the tubercle bacillus may, of course, be taken as pathognomonic, whilst the effects of mercury and iodide of potassium in syphilis and their lack of action in glanders are held to justify a diagnosis. Chronic pyæmia is not, as a rule, difficult to diagnose, if any history of the case can be obtained. (*Vide* vol. i. p. 888.)

On comparing the acute and chronic conditions it will be recognised that the *acute* disease is characterised by many of the features of the chronic form, the main difference being that in the one the processes are distributed over a much longer period than they are in the other. The acute form is almost invariably fatal when the lungs, the gastro-intestinal tract, or the kidneys are affected.

Formerly the diagnosis between glanders and the various coccal pyogenetic infections, bacterial suppuration and the like, was a matter of some difficulty. The other diseases for which it is most frequently mistaken are rheumatic fever, influenza, and typhoid fever, especially as in the latter disease periostitis may occur. This condition, however, does not come on until a comparatively late stage in any case of typhoid fever. The cultural and injection methods now adopted are usually sufficient to enable a diagnosis to be made in most of these doubtful cases, though it must be remembered that in the later stages of glanders streptococci may be found living in association with the glanders bacillus.

Treatment.—Acute farcy in man, unless it is strictly localised, is of comparatively slow onset, and invades none of the internal organs, is so

uniformly fatal that treatment is of little avail except for the protection of others; in chronic farcy, however, from which some 50 per cent of the cases recover, although very slowly and after a very tedious and disappointing course, numerous methods of treatment have from time to time been adopted: iodide of potassium, aconite, mercury, iron, arsenic, and strychnine have all been used in turn, but with little or no good effect. The mercurial treatment is said to bring down the fever, but it exerts little influence in stopping the spread of the disease. As regards prevention in both acute and chronic cases, the patient and his friends, or, in the case of the horse, those dealing with the affected animal, should be warned of the danger of infection by the discharges from the wounds, nostrils, etc. These wounds should be washed with $\frac{1}{1000}$ corrosive sublimate, and covered with a dressing soaked in a similar solution. Any wounds smeared with discharge from a glandered subject should be washed at once with corrosive sublimate and then cauterised with a thermocautery. Dr. Bendall considers that the best treatment, especially in the earlier stages, is local destruction of the primary sore, the application of chlorinated or similar lotion to the mucous membrane of the nose, and tonics. He adds, however, "in a future case I should open every abscess as it appeared, and administer benzoate of soda at frequent intervals." Curetting of the abscess and of all nodules as they are formed, and stuffing with iodoform after washing out with 5 per cent carbolic acid, is also strongly recommended. Nicolaier suggests the poulticing of hard phlegmonous parts with acetate of aluminium, and Garré cauterises the ulcers of the nasal mucous membrane with zinc chloride; while without, or in conjunction with, this treatment a spray or douche of permanganate of potash or insufflation of iodoform and tannic acid should be tried. Bonome recommends the use of carbolic acid in the same way, and there can be little doubt that some such treatment would probably be useful. Bonome, also following Babes, has used mallein in the treatment of chronic glanders in man. He found that injected in doses of two or three drops it was followed by a rise of temperature, then by swelling of the mucous membrane of the eyes and nose, increased frequency of the pulse, and an increase in the excretion of the urine; the respiration remained normal. After several injections these symptoms became less marked; the local œdematous painful swelling, at first a marked feature, soon disappeared; the temperature gradually became subnormal, and there was great polyuria; but no albumin or sugar appeared in the urine. The continued injection of $\frac{1}{20}$th to $\frac{1}{15}$th c.c. of mallein, at intervals of two or three days, was followed in a couple of months by marked improvement, less swelling, healing of the ulcers, diminution in the amount of nasal discharge, and general improvement of the patient's condition. Glandered horses treated in the same way gradually lose the nasal discharge, and the swelling of the glands disappears, and so also do the ulcers of the nasal mucous membrane. Sir J. M'Fadyean, who has kept horses undergoing such treatment under observation over considerable periods, has observed that both the local and temperature reactions gradually become less

marked and ultimately disappear; how far these improvements are permanent still remains to be seen. This has not been confirmed by Zieler. Nocard states that he has demonstrated that in horses and dogs a primary infection successfully surmounted does not increase the powers of resistance to the glanders virus, *i.e.* one attack confers no immunity against a second. It is now accepted by most veterinary surgeons that in cases of chronic glanders an animal that is placed in good hygienic conditions, is well fed, and not overworked, is much more likely to recover than an animal not so conditioned, and it can hardly be insisted on too strongly that the human subject, to have the best chance of recovery, must be placed in similar favourable conditions, especially as regards nourishing food, rest, and fresh air. In all cases in which there appears to be improvement for a time, it must be remembered that there is a temporary "weakening" of the disease, and that ulcers and abscesses may come to a standstill, and even apparently heal (as in certain experiments that have been carried out with immune serum), and then break out again, shewing that the patient has not been cured. Indeed, as quoted above, a horse that has recovered from one attack is found to possess no greater immunity against a second attack than an "unprotected" animal. Serum from an immune animal, horse or cow, is said, however, to exert a certain immunising or protective influence on cats and guinea-pigs, causing prolongation of the disease and putting off the death of the animal from five to twenty-one or even forty-two days. Moreover, donkeys treated with mallein and then with dead glanders bacilli are said to yield a curative and protective serum. It appears that up to the present, nothing more than a very transitory immunity has ever been obtained by the use of anti-mallein serum in horses. Although an effective immune serum will continue to be eagerly sought and studied, early surgical interference with the knife, sharp spoon, and cautery, nourishing food and antiseptic and palliative drug treatment constitute up to the present the main agents in the treatment of glanders and farcy.

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ANTHRAX

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SYNONYMS.—*Splenic fever ; Wool-sorters' disease ; Malignant pustule ; Anthracæmia ; Charbon ; Anthrax malin ; Milzbrand ; Mycosis intestinalis.*

Short Description.—A specific, highly contagious, and infectious disease, common to man and most vertebrate animals, due to the presence of the *Bacillus anthracis* in the tissues of its host. At the points of introduction it multiplies rapidly, and is conveyed by the blood- and lymph-streams to other parts of the body ; by its enormous numbers it blocks the capillaries, causing innumerable hæmorrhages in the organs and tissues, and effusions into the serous cavities and cellular tissue ; and by its special toxic products it produces great depression of all vital functions, which often ends in death within a few days.

History.—Anthrax has been known from early historic times. The descriptions given in Biblical and ancient classical records of devastating plagues among domestic animals correspond very closely with those of some destructive epizootics which spread over the continent of Europe during the Middle Ages, and also with others of more recent times, which, although they did not cover such extensive areas of country, destroyed vast numbers of animals, and are known to have been anthrax.

It was not until near the end of the sixteenth century that this disease was suspected to be communicable to man by contagion from animals. The seventeenth and eighteenth centuries were remarkable for the widespread devastation caused by it throughout Europe ; and, although it was well known to veterinarians at that time, it was not until towards the close of the eighteenth century that the disease in man, which had previously been considered as carbuncular, was known to be the same as charbon, which was so prevalent among cattle, and to be communicable from them to man. In his book on *Anthrax in Animals*, published in 1780, Chabert first distinguished the different forms of anthrax from other septic and gangrenous diseases of the skin which had been included under the same name. He, however, failed to recognise symptomatic anthrax (black quarter, Rauschbrand) as a distinct disease. From his time little advance was made in our knowledge of this disease—save that its contagiousness in animals was proved experimentally by Barthélemy in 1823—until the appearance of the classical work, mainly on the epidemiology of the disease in animals and man in all

parts of the world, by Heusinger (22) in 1850. In 1886 Wilhelm Koch gave a detailed summary of the knowledge gained up till then on anthrax, in a book which is especially valuable for the full references it contains to the previous literature of the subject.

Bacteriology.—The important discovery of the *Bacillus anthracis*, which is the immediate cause of the disease, was made in the year 1850 by Rayer and Davaine conjointly. They described "little filiform bodies, in length double the diameter of a blood-corpuscle, and having no spontaneous movements," in the blood of animals that had died of splenic fever; but they failed to recognise their importance. In the year 1855 Pollender published a statement that he had in 1849 noticed a countless number of fine non-motile straight rods without branches in the blood of cattle that had died of anthrax. He asserted the vegetable nature of these bodies, but gave no explanation of their origin. Brauell in 1857 noticed similar bodies in blood which had been taken a few hours before death from a man suffering from anthrax. With this blood he inoculated horses and sheep, and thus produced in them anthrax, from which they died; he did not, however, ascribe any importance to these bodies as a cause of anthrax. Delafond, in 1860, noticed that this organism, when it developed outside the animal body, assumed the form of long, undulating filaments, as distinguished from the short, straight rods seen when it grew within the living body; he further asserted his belief that they originated from spores. During the following few years Pasteur's brilliant researches into the importance of the influence of microbes in fermentation, putrefaction, and various forms of disease, stimulated others to work in the same direction. In 1863, Davaine (11) resumed the investigations which he had discontinued thirteen years before. These researches were carried on for many years, till in 1873 he asserted positively that these rods, which he called *bactéridie du charbon*, were the essential cause of this malignant disease; that they were constant in the blood of animals that died from anthrax, and that such blood when filtered and inoculated in animals had no effect. This was confirmed by R. Koch (23), who in 1876 worked out the life-history of this bacillus. By developing the method of cultivation on solid media outside the body, he succeeded in cultivating the bacilli, and in proving the formation of spores; he also demonstrated that bacilli might be developed from spores. Finally, from the organism thus cultivated he produced the disease by inoculation in animals. These results were afterwards confirmed by Pasteur, who, in 1877, demonstrated beyond all doubt that these small rod-like bodies, first recorded by Rayer and Davaine in 1850, were the sole cause of this disease.

1. *Physical Characters.*—As seen unstained in the blood of animals shortly after death by anthrax, the bacilli are pellucid, round, elongated, rod-like cells, 4·5-10 μ in length, but commonly about the length of the diameter of a red blood-corpuscle, and from 1·0-1·5 μ in breadth. In fresh material the bacilli are usually isolated; sometimes they lie in

groups of two or three. They are motionless, and contain a homogeneous protoplasmic material enclosed in a fine capsule of denser and more highly refractive substance. Special staining shews that the cylindrical bacillus enclosed in its capsule is transversely divided into two or three segments. In a suitable nutrient medium, at a temperature of about 37° C., they increase in length, the contents become slightly opaque and granular, and at regular intervals slight swellings of the rods are noticed; at these points the protoplasm appears to collect, becomes more refractive, and presents a well-defined outline which is its capsule; the rod between these bodies, which are now slightly ovate, bright and highly refractive, becomes contracted and separates. The spores thus freed elongate at each end, and in two hours grow into bacilli which pass through similar processes of development and decay. The anthrax bacilli stain readily with watery solutions of fuchsin, methylene blue, and gentian violet, and by Gram's method. Several methods are described for staining the spores. Results are most likely to be successful with fresh material.

2. *Growth and Development.*—The organisms are aerobic; they cannot live without oxygen. They do not grow below 12° C. or above 45° C., but they multiply most rapidly between 30° and 40° C. in a neutral or slightly alkaline medium. In the living blood they are parasitic, and can abstract from the blood sufficient oxygen to maintain their propagation, but not to enable them to grow into long filaments or form spores. In the dead body they grow to a great length without shewing lines of transverse segmentation, and with the formation of a few spores only. Outside the body, when they can obtain a free supply of oxygen, they pass through their complete cycle of life and form spores, thus indicating their saprophytic origin. In unopened putrefying carcases they degenerate and die in about a week; in the earth they retain their form, but generally lose their virulence in six months.

Luxuriant growth takes place not only on the usual culture media, but on numerous foods, provided they are neutral or slightly alkaline. R. Koch shewed that infusions of hay or of seeds rich in starch, such as barley, wheat, pulse, and grass, when neutralised or made slightly alkaline, formed suitable soils. Culture in broth for twenty-four hours produces a flocculent aggregation of bacilli at the bottom of the glass, and microscopically the bacilli shew long, undulating, thread-like formations. Plate-cultures on gelatin and agar at 18°-20° C. in two to three days shew characteristic colonies—a tangled mass of threads with wavy processes extending into the medium from the central mass. The gelatin is gradually liquefied, and the colonies sink below the level of the unliquefied portions. In stab culture in gelatin or agar delicate white rays grow outwards and penetrate the medium laterally, looking like thistle-down, growth being most luxuriant in the upper portions, while in the case of gelatin liquefaction proceeds slowly from above downwards. On potato growth is luxuriant with early formation of spores. On sloping blood-serum anthrax bacilli develop as a whitish-grey scum with slow liquefaction of the medium.

Asporogenous varieties of anthrax bacilli can be developed by culture in the presence of some agent (usually chemical) inimical to normal growth. Virulence may not be apparently affected, but even passage through animals will not bring back the power of sporulation. The resistance of different strains of bacilli may vary greatly. While bacilli are killed comparatively easily, the spores are very tenacious of life, especially when surrounded by grease, dirt, or dried blood as in horse-hair. As a rule, the bacilli are killed by exposure to 55° C. for forty minutes; spores by steam at 95° C. in ten minutes, by current steam at 100° C. in five minutes, and by hot air at 140° C. after three hours. Light, especially direct sunlight, affects the vitality of the bacilli, and robs the spores of their power of development into bacilli more readily than it deprives the bacilli of their power of multiplication. Corrosive sublimate, 1 in 10,000, prevents the growth of anthrax bacilli, and 1 in 1000 kills spores in one hour. A 1 per cent solution of formalin is said to destroy spores in two hours, a 2-5 per cent solution in one hour, and a 10-20 per cent solution in ten minutes; 1 in 20,000 solution inhibits the growth of bacilli.

The *Bacillus pyocyaneus* exercises a remarkable retarding influence on the growth of anthrax bacilli when the two are grown together in bouillon or on agar. From this bacillus a substance, pyocyanase, has been obtained which dissolves anthrax bacilli *in vitro*, and shows bactericidal properties in the animal body. It has been used with success in the case of rabbits infected with anthrax.

3. *Attenuation.*—Toussaint first (1880) successfully produced artificial immunity in sheep against anthrax by inoculation (after heating at a temperature of 55° C. for ten minutes) of 3-6 c.c. of the blood of animals which had died of anthrax. Since 1881 Pasteur and Chamberland's modification of this method—inoculation with two vaccins, *i.e.* cultures attenuated in different degrees, at an interval of twelve days—has been carried out on an enormous scale as a prophylactic against the disease in sheep and cattle. The attenuation reached by keeping cultures at 42° to 43° C. is such, that after twenty-four days (the first vaccin) mice succumb to inoculation, but guinea-pigs as a rule do not, whereas after only twelve days (the second vaccin) guinea-pigs succumb, while rabbits similarly inoculated generally survive. Sobernheim (45) gives the following figures as showing the extent of the treatment by Pasteur's method:—Up to January 1, 1900, the number of animals that had been inoculated exceeded 11 millions. In France alone 250,000 to 350,000 sheep and 30,000 to 50,000 cattle and horses are thus treated yearly. In Hungary, in the twelve years 1889 to 1900, 718,266 cattle were inoculated, of which 174 (0·02 per cent) died between the two inoculations, and other 144 within a year. Among 1,247,231 sheep the deaths between the inoculations were 0·26 per cent, and within a year 0·33 per cent. Reference to the production of active and passive immunity and serotherapy will be found on p. 252 under the heading "Treatment."

Anthrax in Animals

Anthrax is the most widely spread and the most destructive of all contagious diseases which affect animals. It is found in all countries, but is much more prevalent and persistent in some than in others, and in some districts of these countries more than in others. It is extremely prevalent in parts of France, Germany, Italy, Turkey, Russia, throughout Asia, North Africa, and South America; and is least prevalent in Australasia, South Africa, and North America. During epizootics it may be fatal to from 50 to 70 per cent of the cattle, horses, or sheep of a district, besides sometimes carrying off a large number of the population.

The following official figures shew the reported number of animals attacked in 1904:—Great Britain 1553, Germany 5959, Italy 3946, European and Asiatic Russia 28,913.[1] In that year in Germany 0·24 per 1000 of the total cattle were affected. Anthrax districts, "champs maudits," are areas in a country where the disease is constantly recurring. River valleys, owing to liability to flooding, soils rich in organic and mineral matter, such as prairies, steppes, moors, and marsh-land, are often anthrax districts. Height above the level of the sea has little influence, but a definite temperature in the soil, *i.e.* between 18° and 40° C., must be reached before saprophytic growth of the bacillus and formation of spores can take place. Thus, in European and Asiatic Russia, where the figures quoted shew there is great mortality among animals from anthrax, the number of animals attacked in each of the winter months (November to March) rarely exceeds 1000, but with the summer this mounts up rapidly, and may exceed 17,000 in July and August. This seasonal curve in the figures of incidence of anthrax is observed in other countries, such as Italy and Germany, with high summer-temperatures, but is absent in the returns for Great Britain.

All classes of vertebrate animals are susceptible to anthrax. The herbivorous mammals, such as cattle, horses, camels, alpacas, sheep, goats, and rodents, readily catch the disease. Some of these (as cattle) are very susceptible to intestinal infection, and less to the subcutaneous inoculation; others (as guinea-pigs and white mice) are rarely infected through the alimentary canal, but very readily by experimental inoculation. Some breeds of animals (as Algerian sheep) are but little susceptible, and do not take the disease spontaneously. The omnivorous mammals—such as pigs, dogs, cats, and rats—are less susceptible. The carnivorous can only be infected in favourable circumstances as regards age, alimentation, and the virulence or quantity of the material inoculated. Birds, reptiles, and fishes are relatively immune; but if the high temperature of birds be diminished and the low temperature of reptiles and fishes raised by artificial means, they can be infected. Anthrax ordinarily attacks animals by way of the intestines. The pulmonary form in them is

[1] The figures for Russia in 1904 are probably inaccurate on account of the Russo-Japanese war. The figures in 1903 were 52,473, and in 1902, 51,425.

acquired only by experimental inhalation of virulent spores. Subcutaneous inoculation of anthrax virus produces locally a gelatinous swelling of the cellular tissue, but never anything like the cutaneous variety in man.

The disease does not spread by contact or association; it can only be acquired in ordinary circumstances by the introduction of the infecting organisms into the circulating blood, either through an abrasion or defect of the mucous membrane, or by the spores otherwise finding their way through the epithelium of the alimentary canal, and so causing a general infection. Although "splenic apoplexy" has been known in this country from a remote period as the cause of a large mortality among cattle, it is only since the year 1859 that it has been recognised as anthrax. Since 1886 the disease has been included in the list of maladies which come under the provisions of the Contagious Diseases (Animals) Acts. These are administered by the Board of Agriculture, which prohibits the importation of live animals from infected foreign countries.

In the ten years 1895-1904 the number of reported outbreaks in Great Britain was 6161, and of animals attacked 8252 (cattle 7071, sheep 598, swine 185, horses 398). During this period there has been an apparent marked increase in the disease from 434 outbreaks in 1895 to 1049 in 1904. Prof. Delépine has shewn from figures for the years 1897-1902 that the distribution of anthrax in the various agricultural divisions is not essentially determined by geographical situation, climate, density of cattle population, or extent of manured land. He and others also have studied the important point as to how far the extensive industries in this country, involving manipulation of raw wool, horse-hair, hides, and skins, affect the incidence in cattle from access of spores in waste-water to streams, or from the use as manure of the refuse dust from these factories. The high number of outbreaks in the West Riding of Yorkshire, the centre of the woollen industry, and in Northamptonshire, the centre of the leather industry, suggests a causal connexion, but reduction of the number of outbreaks, or of animals attacked, to a rate on the number of animals in the several counties, negatives any sweeping conclusion that incidence in animals corresponds at all closely with the distribution of factories manipulating raw animal products.

Anthrax, in proportion to the number of cattle in Scotland in 1904, was three times as rife as in England, although cases of human anthrax of industrial origin in the seven years 1899-1905 numbered 304 in England and only 14 in Scotland. The counties with the highest incidence of anthrax in proportion to the number of cattle (1899-1903 figures) are Haddington, Elgin, Aberdeen, Forfar, Banff, Perth, Westmorland, Northumberland, and Hertford, and in them, probably, infected areas have been created from inadequate disposal of the carcases of animals that have died of the disease. Recently Sir J. M'Fadyean has brought artificial feeding stuffs, the raw material of which is derived from foreign countries, under suspicion, and in one outbreak he isolated the bacillus from the linseed-cake used. Cases of anthrax in man at ports

both in this country and in Hamburg from the unloading of grain have been sufficiently numerous to direct attention to the possibility of the introduction of the spores in the particles of soil adhering to the grain.

Despite what has been said, serious outbreaks among cattle have in several instances been traced directly to infection of meadows either from flood-water dispersing anthrax spores originally contained in raw materials dealt with in factories, or from refuse from them used as manure. As shewing the resistance of anthrax spores to the influence of tanning, liming, arsenicating, and other processes, Dr. C. A. Houston has demonstrated the presence of anthrax in (1) the effluent from the final catchpit in a skin factory at Yeovil, (2) in the septic tank liquor, the sludge, and the washings of coke from primary and secondary coke-beds, and (3) in the mud from the banks of the River Yeo and the Yeo brook.

The Governments of Europe and of many other countries enforce measures to control the spread of this disease. The most important of these in Great Britain are—(1) Notification of the outbreak to the Local Authority, (2) Isolation of animals that have been in association with the dead animal, and prohibition of the movement of animals from localities in which anthrax has broken out to other districts, (3) Disposal of the carcase unopened, (4) Disinfection of infected premises. To carry out (3) the Board of Agriculture recommends cremation, or, when this is not possible, burial deep in the ground with the addition of lime. Since the chief cause of the spread of infection is the concealment or overlooking of cases, Professor Delépine suggests that all cases of death from acute illness or cases of illness rendering slaughter at the farm necessary should be notified. The prophylactic use of Pasteur's vaccins is referred to on p. 254.

Anthrax in Man

Nomenclature.—Deaths from anthrax were first separately recorded in the Annual Reports of the Registrar-General in 1863, under the heading Malignant Pustule; since then, also as Charbon, Wool-sorters' Disease, and Splenic Fever. Now (1906) they appear as anthrax (splenic fever). The word pustule is at the present time restricted to those elevations of the tissues which contain pus. The name "malignant pustule" in this connexion is inappropriate and misleading, because the disease is often not malignant, and its "pustule" never contains pus. The disease in all its aspects is most widely known as "Anthrax," and the general infection as "Anthracæmia." It is desirable that the names "malignant pustule," "wool-sorters' disease," "mycosis intestinalis," and others (appropriate enough when the nature of the disease was unknown) should be discontinued, and that the term "anthrax" be substituted. The different forms assumed by it would then suitably be described according to the part of the body through which the virus gains access to the blood, as:—

(1) *Cutaneous Anthrax.*—This is the most widely prevalent form, and presents two varieties: (*a*) Necrotic anthrax—"malignant pustule" or vesicle. This results when the bacilli or spores have been introduced through an artificial opening, the local lesion thus produced having a necrotic centre with surrounding vesicles and inflammatory swelling. (*b*) Erysipelatous anthrax, of which œdematous anthrax—*œdème malin* of Bourgeois—is a milder representation. This results when the virus has passed through imperceptible or possibly natural openings. (2) *Pulmonary Anthrax*—"Wool-sorters' disease." In this form and in (3) *Gastro-intestinal Anthrax* there is no external lesion. The first is often spoken of as external, and (2) and (3) as internal anthrax.

Etiology.—The immediate cause of all forms of anthrax is the introduction of the *Bacillus anthracis* or its spores into the living tissues and blood current. The disease occurs—1. In those who come into contact with living animals suffering from anthrax, as drovers, shepherds, farmers, farriers, and veterinary surgeons. 2. In those who touch the carcases of animals that have died from anthrax, as knackers, slaughterers, butchers, and inspectors of meat. 3. In those who handle offal, skins, hoofs, horns, hairs, wools, or other derivatives from diseased animals, such as tanners, fell-mongers, wool-workers, hair-workers, horn-workers, rag-sorters, plasterers, furriers, felt-makers, brush-makers, mattress-makers, and so forth. 4. In those who have no direct connexion with infective materials—who live, for instance, in the neighbourhood of such manufactories. In countries where the disease is common among animals, women and children are not infrequently attacked with the disease through the medium of persons, animals, or insects. 5. It has several times been transmitted from one person to another with fatal results—as at a post-mortem examination. A wife is also reported to have taken it by touching her cheek with her hands when dressing the sore of her husband. In some undoubted cases the source of the infection cannot be traced.

Among all countries of the world Great Britain is exceptional in that anthrax in man is mainly of industrial origin, *i.e.* arises much more from spores contained in material imported from distant countries than from contact with the carcase of an animal that has died of the disease. No official figures are published of the number of farm labourers or slaughtermen attacked, but it is stated that in connexion with 7 out of 460 outbreaks of cattle anthrax into which the veterinary officers of the Board of Agriculture inquired between the months of July and December 1904, twelve persons contracted the disease, of whom six died. The number of cases of anthrax contracted in a factory or workshop (notified to the Chief Inspector of Factories in pursuance of section 73 of the Factory and Workshop Act, 1901), during the years 1899-1905, was as follows:—

Industry.	Males.	Females.	Total.	Fatal.	Per cent.
Worsted and wool . .	95	27	122	35	28·7
Horse-hair and bristles .	56	21	77	18	23·4
Hides and skins . .	103	...	103	25	24·3
Other industries . .	16	2	18	7	38·9
	270	50	320	85	26·6

The varied nature of the occupation of the persons thus reported is shewn in the following table, which is arranged, as far as possible, in the order of the processes of manufacture from the time the material is received in the bale to that when it leaves in the finished condition :—

Wool

Wharfinger	1	Carder and comber . . .	29
Vanman	1	Finisher and preparer . .	7
Warehouseman	4	Packer	3
Overlooker	1	Spinner and weaver . . .	7
Occupier	1	Waste-puller	1
Wool-steeper	1	Sweeper of floors . . .	1
Bale-opener	7	Dyer	1
Sorter	20	Engineer	1
Willower	15	Mechanic	1
Blender	4	Infected outside factory . .	4
Wool-washer and wool-runner .	11		
Dryer	1	Total	122

Horse-Hair

Vanman	1	Brushmaker	16
Clerk in office	1	Yarn-winder	1
Warehouseman	4	Stuffer of boxing-gloves . .	1
Opener, weigher, and carrier .	10	Stuffer of mattresses . . .	1
Washer	1	Wet heckler	1
Sorter and mixer . . .	4	General work	1
Willower	8	Infected outside factory . .	4
Drawer and dresser . . .	12		
Curler and carder . . .	11	Total	77

Hides and Skins

Dock labourer	21	Portmanteau-maker . . .	1
Wharfinger	44	Leather-seller	1
Fellmonger	1	Maker of picker-straps . .	2
Tanner	29		
Bootmaker	4	Total	103

Other Industries

Dock labourer	2	Vanman	1
Fruit and vegetable warehouseman	2	Worker in mother of pearl	1
Horn-worker	2	Knife-hafter	1
Rag-sorter	1	Unloader of grain	1
Linen-weaver	1	Grain dealer	1
Chemical manure-maker	1	White-lead worker	1
Saddler	1		
Railway porter	1		
Worker in harness furniture	1	Total	18

So far as could be ascertained, the country whence the wool, horse hair, and hides and skins originated was as follows :—

Wool.		Horse-hair.		Hides and Skins.	
Persian (Bagdad)	38	China	25	China	19
Persian or camel hair	7	Russia, Siberia, or China	13	China or East Indian	5
Persian or alpaca	1	Siberia or Russia	5	Madagascar, East India, or China	1
Mohair, camel hair, or Persian	3	South America, Siberia, or Russia	13	Bombay, East Indian	21
Mohair	15	All kinds except Chinese mane hair	6	East Indian or Russian	1
Van mohair	8	Indefinite	15	Cape or Straits Settlements	1
Van mohair, alpaca, or Cape mohair	2	Total	77	Cape	3
Van mohair or Persian	3			Cape or Australian	1
Mohair or Cashmere or camel hair	2			South American	1
Cape mohair or Turkey mohair	5			Australian	1
Mohair, camel hair, or alpaca	3			South American or New Zealand	1
East Indian	13			Arabian	1
Native, Colonial, or East Indian	3			Morocco	2
Camel hair	6			Morocco or East Indian	1
Camel hair, East Indian or alpaca	2			West African	3
Alpaca	1			Straits Settlements	5
Probably Persian or East Indian	2			Madras and Bombay tanned hides	1
Indefinite	8			Tanned sheepskins	2
Total	122			Tanned boot-leather	4
				Native	1
				Colombia	1
				Persian, China, and Cape goatskins	4
				Indefinite	23
				Total	103

Although the amount of wool imported from Australasia is about double that from the rest of the world, no case of anthrax has with certainty been proved to have arisen from its manipulation. This has been attributed to the amount of "yolk" or natural potash soap contained in Australian wool, the presence of which would lessen the

diffusion of dust. Asiatic, Egyptian, and other low class wools from warm climates are dry and dusty, because of the relatively small amount of "yolk" in them. Probably far more important factors than this are the acknowledged small incidence of the disease in Australia and New Zealand, the precautions there taken to prevent the spread of the disease, and the proper disposal of carcases of animals that may have died. In Asia Minor and Persia no precautions of this kind are taken, and manufacturers in this country report of Persian wool that nearly every bale is falsely packed, that is, the fleeces contain locks (inferior wool), skin, wool of animals that have died of disease, cotton rags, besides soil, sand, dirt, and dust.

The cutaneous type of the disease was known to Arabian, Egyptian, Greek, and Roman medical writers, some of whom describe the various stages of the disease with great accuracy. Its frequent transmission to man from the handling of hairs and wools was first pointed out in 1769 by Fournier. Montfils in 1776 recorded similar cases. Rayer in 1835 published three cases, one in a person who was attacked after cleaning Russian horse-hair which for many years had served as stuffing for an easy-chair. Trousseau in 1847 described cases occurring among workers of horse-hair imported from Buenos Ayres. It does not appear to have been known as anthrax in England before Budd's accurate description of malignant pustule (anthrax) in 1862. Among workers in hides and skins the pulmonary form has occurred so rarely that only two cases are recorded. Among horse-hair workers the cutaneous form has been and is still predominant. Cases of the pulmonary or internal form from manipulation of horse-hair have been recorded in the past, notably by Dr. J. B. Russell in an epidemic in Glasgow in 1878, when nine persons were attacked, of whom seven (three fatal) were believed to have contracted the disease in the internal form; and later in 1893 by Chauveau. None of the cases reported to the Chief Inspector of Factories as having been contracted in horse-hair factories since 1899 have assumed the internal form. In the worsted and woollen industry the prevailing form at the present time is cutaneous, but formerly it was pulmonary. Of this there can be no doubt, and it is important to find an explanation of this alteration in type. The disease was first noted in the Bradford district after the introduction of alpaca and mohair as textile materials in 1837. Occasional unusual illnesses and sudden deaths occurred among the sorters of these wools. At Queensbury in 1846 several deaths occurred within a short time. Again in 1853-1854 there was an outbreak which caused considerable alarm. In 1867-1868, and again in 1874, many deaths of wool-sorters occurred at Saltaire, where alpaca and mohair were largely used. In November 1879, when attending a wool-sorter—who died twelve hours afterwards—one of us (J. H. B.) withdrew some blood from the arm, and within a few minutes injected two or three drops of it under the skin of a rabbit, a guinea-pig, and a white mouse respectively. The animals all died within sixty hours, and the blood of each shewed the presence of bacilli. Another animal was

inoculated with blood from one of these, and it died in a shorter time. The fluids from this animal were found to be crowded with *Bacillus anthracis*, and the disease was recognised as anthrax. During the year 1880 Mr. J. Spear, with whom was associated Professor Greenfield, investigated the subject of wool-sorters' disease on behalf of the Local Government Board. He dealt in his report with 32 cases, of which 23 (19 fatal) were of the internal, and 9 (2 fatal) of the cutaneous type. Internal anthrax was, he wrote at that time, "the form of the disease which is the much more common one, at all events the more commonly recorded one amongst wool-sorters." In the former edition of this article (1896) the pulmonary form was still considered the commoner, and it was stated that "in the Bradford worsted district 30 cases of external and 57 cases of internal anthrax have been recorded." During the seven years 1899-1905, however, only 13 cases (all fatal) of the internal form have been reported, as compared with 60 of the cutaneous. Some explanation of the change may be found in the more frequent diagnosis now of the external form, and inclusion under this head of the erysipelatous form; but this is insufficient to explain the very great reduction in cases of true wool-sorters' disease. One circumstance, however, has been materially modified within the last twelve years, namely, the manipulation of the wool by localised exhaust ventilation referred to on p. 255, and this we regard as the main cause of the alteration in type.

Workers in the woollen and worsted industry in Germany and France apparently escape anthrax in any form. Danger from anthrax of the cutaneous type, but never of the internal, is well recognised, and many outbreaks have been recorded in the manipulation of hides and skins and horse-hair. In Lower Austria, however, Eppinger[1] has described 88 cases (78 fatal) of anthrax among rag-sorters in certain paper factories between 1870 and 1886 as having been all of the pulmonary or internal type. Very rarely a sporadic case of anthrax occurs among rag-sorters in the West Riding.

The intestinal form of anthrax in man is extremely rare; only two cases have been recorded in this country. Wahl described the first case in 1861, a second was reported by von Recklinghausen in 1864. Buhl in 1868 described cases with hæmorrhagic infarcts in the stomach and intestines, very like the lesions seen in the bowels of horses dead from splenic fever. In 1871 Waldeyer met with such cases. Münch of Moscow, in 1871, first determined the anthrax nature of this disease which he had found in hair-workers with internal lesions similar to those noticed by Wahl and Buhl. Since then other cases have been recorded; but no doubt many have been cases of pulmonary anthrax with secondary intestinal infection. This form is to be anticipated from the consumption of bacilli in infected meat, and such food must necessarily be regarded as

[1] Professor Eppinger, in a letter dated January 13, 1906, has informed us that since 1894 only two cases have been reported from these paper factories—one cutaneous which terminated fatally, and the other pulmonary ending in recovery. Bacteriological examination and animal experiment in the last case were negative.

dangerous, although from the numerous instances that are known where such food has been eaten without injurious effects the great majority of the bacilli must be destroyed by cooking.

The cutaneous form may develop at any point on the skin, although it is very rare on the fingers or thumb in this country. The situation in 299 of the reported cases (1899-1905) was as follows :—

Situation.	Number.	Per cent.
Head and face . . .	129	43·1
Neck	123	41·1
Upper extremity . . .	40	13·4
Lower extremity . . .	3	1·0
Trunk	4	1·3

This list refers to cases in which infection is mainly due to dust. If contracted by persons from contact with the carcase of an animal that has died from anthrax the lesion will be found much more frequently on the forearm or hand. There is usually only one point of inoculation; occasionally two or more are seen; the lesions progress simultaneously.

It is doubtful whether one attack confers any protection against a future attack; second attacks are recorded.

PATHOLOGICAL ANATOMY.—**Cutaneous Anthrax.**—*Local.*—During the first few days the changes in the skin at the point of inoculation are those of acute inflammation, followed by fibrino-serous exudation and central necrosis. The black eschar, consisting of epidermis including the Malpighian layer, is depressed, and does not extend deeper than the skin. The epidermis around may be detached, and the dermis appear of a dirty yellow-grey or a reddish-purple colour. The exudate contains red blood-cells, a few leucocytes, the *Bacilli anthracis* and often other organisms. The papillæ are swollen, and the interspaces filled with leucocytes and *Bacilli anthracis.* The bacilli are irregularly distributed, but are most numerous near the eschar, beneath the adherent epithelium in the Malpighian layer. In the superficial layers of the skin, after a few days, other bacteria are found. In the deeper layers there are very few bacilli; they do not extend in great numbers more than two inches beyond the eschar. They are not found in the adipose tissue beneath. The brawny swelling when cut may be crowded with punctiform hæmorrhages.

General.—The states of the various organs are in great measure similar to those found after death from all forms of anthrax, the local lesions predominating according to the part inoculated.

Pulmonary and Gastro-intestinal Anthrax.—*External Changes.*—The discoloration of decomposition appears very soon; it is of more than the usual lividity, and is not confined to the posterior part of the body. Within two to four hours the lips, ears, neck, upper part of the chest,

and shoulders are of a dark-purple colour, the nails of a black-blue colour, and the exposed skin of the penis and scrotum claret-coloured. Occasionally there is no unusual discoloration of the skin. There may also be minute purple spots on various parts, more frequently on the chest and abdomen. Dark chocolate-coloured fluids issue from the mouth and nose. The cellular tissue in front of the neck and upper part of the chest is sometimes swollen and emphysematous.

Internal Changes.—The external muscles of the chest on section are often dark in colour, except where there is much œdema. On removing the sternum the cellular tissue beneath is sometimes emphysematous, and bubbles of gas escape; at other times there is considerable gelatinous œdema of the cellular tissue; occasionally it has been seen to be extensively infiltrated with blood. The pleural cavities almost invariably contain a large quantity of clear, straw-coloured serum; often two to four pints in each side—generally most in the right side. Any inflammatory lesions of the pleuræ are due to accidental causes. The anterior surface of the lungs may appear normal; or the gelatinous œdema under the serous covering may be as much as one inch in thickness at the most dependent parts, and may extend between the lobes without any plastic inflammatory exudation. Under the serous coat are often numerous small patches of ecchymoses. On section the lungs are engorged with dark-coloured blood, the right more so than the left; the posterior and lower parts are more congested and œdematous; some portions are more solid than others, and of a blacker red colour. It is not uncommon to find extravasations of blood—of any size up to that of a walnut—in the lungs; and in prolonged cases the larger of these appear to become purulent.

The bronchial glands are generally, not invariably, enlarged; they are usually larger on the right side, and may be the size of a hen's egg. They are hard, easily broken down by the thumb, and filled with dark-coloured blood. The trachea and bronchial tubes contain frothy, blood-stained mucus; the mucous membrane of the trachea and of the larger bronchi is stained a claret colour and is swollen; beneath it patches of extravasated blood are frequently seen. On a transverse section the lumen is seen to be narrowed by jelly-like, sero-sanguinolent, and hæmorrhagic infiltration. The pharyngeal connective-tissue may be œdematous and infiltrated with blood.

The pericardium at its base may be surrounded by blood diffused in the cellular tissue. It may shew petechial spots or considerable infiltration with gelatinous serum. The pericardial fluid is frequently increased in quantity up to five or six ounces. The epicardium and endocardium show subserous petechial patches, those within the heart at the attachment of the valves being the largest.

The blood is nearly always fluid and of a dark colour, almost black. In a few prolonged cases soft clots are found in both ventricles. The fluid blood produces swelling and engorgement of the internal organs.

The heart is dark-coloured, soft, and flabby; it may be empty, or

contain dark, semifluid blood in all its cavities. The auricular and ventricular septa, and parts of the muscular substance, may even be of a black-red colour from extravasations or staining of blood. The attachments of the cords to the muscular columns of the tricuspid and mitral valves may be similarly discoloured. A dark-red even layer of blood may separate the serous layers of some of the cusps of the pulmonary or aortic valves. The corpora Arantii may be black from ecchymoses. The lining membrane of the heart and larger vessels is stained a hue varying from a pale cherry-red to a dark chocolate, according to the length of time which may have elapsed since death. Very rarely it is not stained.

The abdomen in pulmonary anthrax does not often contain much fluid; but in the intestinal form a considerable quantity may be present. In one case of cutaneous anthrax on the cheek, serum from which had passed into the mouth, the intestines were extensively involved, and four pints of blood-stained serum were found in the abdomen.

The gelatinous œdema noticed in the chest is often found in the abdomen; it may be very considerable in the mesentery, or in the cellular tissue surrounding the kidneys. Extravasated blood in small or large patches may be found under the serous covering of the various organs. Between the layers of the mesentery patches as large as the outspread hand have been seen. There may be much blood also in the cellular tissue around the kidney. When the intestines are affected the mesenteric glands may be much enlarged; in other cases they may be normal. In the stomach and intestines patches of extravasated blood are found under the mucous membrane, and also numerous large congested patches of a mulberry hue several inches long, and often involving the greater part of the circumference of the bowels; or the ecchymoses may be very numerous, small, each with a black centre, and varying in size from the head of a pin to a lentil. The mucous membrane overlying this may be ulcerated; the hæmorrhages when larger appear as subserous on the external aspects of the bowels. In other cases the mucous lining of the stomach and intestines may appear perfectly normal.

The spleen, like all other organs in this disease, varies very much. It is generally larger than natural, but not unfrequently it is unaltered in size or appearance. It has been known to weigh only $3\frac{1}{4}$ ounces. When cut into, if much enlarged, it is diffluent, grumous, and the matter flowing out is almost black. In other cases the organ is soft, pulpy, and in appearance as in other specific febrile diseases.

The liver is less frequently affected than other organs; it appears generally to be normal; but it may be very full of blood; it sometimes presents numerous small hæmorrhagic areas.

The kidneys occasionally shew small extravasations of blood beneath the capsule; the parenchyma is usually engorged with blood.

The brain and spinal cord.—Extravasations of blood not infrequently lie between the membranes, sometimes completely surrounding the brain and filling the lateral ventricles; small infarcts to the size of a pea may occasionally be seen in the cerebral substance.

In a case of gastro-intestinal anthrax described by Dr. Teacher, in addition to many of the pathological conditions here described in the organs, there were found near the pyloric orifice three small swollen hæmorrhagic spots with slightly elevated pustule-like centres. On the surface of the intestines were three or four congested hæmorrhagic areas, and internally, corresponding to the congested patches, were areas of intense congestion with hæmorrhagic sloughy centres. The largest of these was situated about four feet from the pylorus; it consisted of an irregular area about two inches in diameter, deeply congested and infiltrated with extravasated blood. The centre was ulcerated and sloughy, and appeared to be on the point of perforation. The condition was regarded as an acute infection originating at and spreading from this intestinal focus. There was a diffuse hæmorrhagic condition of the pia-arachnoid, which was shewn microscopically to be an early meningitis due to the *Bacillus anthracis.* According to Dr. Teacher, pia-arachnoid hæmorrhage is not infrequently associated with anthrax, and its discovery has sometimes given the first clue to the nature of the case.

The characteristic changes are—(i.) The discoloration of the skin: from this alone in many cases the cause of death may be surmised. In some cases, however, it is not decidedly marked. (ii.) The gelatinous œdema of the cellular tissue in various parts of the body: particularly in the anterior mediastinum, around the pharynx, trachea, base of the heart; in the mesentery, omentum, and fat around the kidneys. (iii.) The extravasations of blood: which may be extensive in the chest, the abdomen, and the head in the same patient; or in only one of these places; with innumerable smaller hæmorrhagic areas in any organ or tissue in any part of the body. (iv.) The extensive serous effusions into the pleuræ, pericardium, and peritoneum.

For the microscopical characters of the tissues in pulmonary anthrax we are indebted to Professor Greenfield's report to the Local Government Board in 1881 on the Wool-sorters' Disease in Bradford. From this report we gather that "the lesion in the bronchi presented in various degrees constant and characteristic features, limited almost entirely to the lower part of the trachea near its bifurcation, to the two main bronchi, and in one case only reaching to the first division. In the earliest stage of the process the most superficial layers of the mucous membrane are found to be infiltrated with bacilli, later they are found in scanty clusters in the somewhat deeper layers, still, however, only in the connective-tissue spaces or in the lymphatics. Very speedily, however, there appear two special conditions, viz. hæmorrhage and inflammation." The hæmorrhage may be slight and only into the subepithelial tissue, which then becomes detached; if more extensive, it may invade the mucous and submucous tissue through their entire depth. In the vicinity of the hæmorrhages is a more marked accumulation of bacilli; they crowd the superficial layers of the mucous membrane, and are found in larger numbers in the connective tissue; masses are also found here and there in the lymphatics, and sometimes in the smaller blood-vessels.

Distribution of the Bacilli.—After inoculation the bacilli spread mainly by way of the lymphatic vessels. The blood can at first only serve as a carrier of the organisms, not as a place for their multiplication. Only at a relatively late period are they to be found in large numbers in the blood when the signs of general infection become prominent. Bacilli are common in the urine of domestic animals when suffering from this disease. In man the kidneys are not very frequently invaded, but when they are, bacilli escape with blood from the capillaries of the glomeruli, and develop in the urine before it is voided from the bladder. Similarly from rupture of capillaries bacilli are found in milk; they will pass also, by rupture of vessels, from mother to fœtus through the placenta. They have been found in the fæces and the sputum.

Incubation.—The period of incubation varies with the method of inoculation and the quantity and virulence of the poison. When it is introduced by the bite of a fly or the sting of an insect, the additional poison immediately arouses a painful itching and rapid inflammation of the skin. Where an inflamed pimple has been scratched and inoculated at the same time, or shortly afterwards, development is almost equally rapid. When the virus is introduced by a cut or abrasion of healthy skin there will be some itching on the following day, with swelling and inflammation on the third day. When the infecting material is fresh and in the bacillary form, incubation will be shorter than when dried spores are the infecting agent. When the period of incubation appears to be longer than two or three days, it is probable that, after exposure to infection, some of the virus has remained about the person or in contact with the skin for several days, or even weeks, without producing any effect; but after it has passed beyond the epidermic barrier it multiplies rapidly, and within twenty-four hours produces its local specific effect.

Symptoms.—1. Cutaneous Anthrax.—(*a*) *Local.*—The necrotic variety is not often seen by the surgeon during the early papular stage. When it proceeds from the bite or sting of an insect there is first a painful itching at the spot, and within a few hours a red papule with a minute central puncture appears; on the following day a vesicle forms with some surrounding redness, and beyond this considerable brawny swelling. When the top of an ordinary pimple has been scratched off and inoculated at the same time—a common event—the spot is very irritable and painful; on the second day there is usually a vesicle, which may vary in size from a split pea to a shilling, and contains a yellow or brown exudation. On the third day the vesicle has burst and shrunk, leaving a grey or brown base exuding serum. On the fourth day there is a *black, dry, depressed eschar*, surrounded by a very characteristic slightly elevated border of small vesicles. The vesicular rim may be indefinite and irregular, or complete; and other red currant-like vesicles on the surface of the adjoining skin may be few and discrete, or many, confluent and extensive. The exudation during life is fluid and often very abundant; after death it may not flow out when the vesicles are opened. When

the eschar extends by including the earlier vesicles, large bullæ form irregularly on the skin around and beyond the margin of the eschar. When there has been a primary anthrax papule on sound skin there may be no red areola, even after the eschar has formed; but there is always a considerable degree of firm œdema of the surrounding tissues, and when there is a mixed infection there will be more redness. The firm, unyielding œdema extends in all directions, and the neighbouring lymphatic glands may be tender, hard, and enlarged. When on the neck the lesion may, within two or three days, involve the larynx, or, much more frequently, the cellular tissue and glands of the mediastinum, and produce dyspnœa and dysphagia. When close to the orbit, the swelling of the eyelids may render the person unable to continue his work, although he may feel quite well. In severe cases the œdema may extend all over the head, neck, and chest to below the nipples. The circumference of the head has been known to reach 29½ inches, and over the eyebrows 26¼ inches. The general absence of pain round the eschar is remarkable; it is never acute, and is rather a sense of weight, fulness, and numbness in the part due to the swelling. There is always an absence of pus till after seven to ten days, when the eschar begins to separate.

The erysipelatous variety appears generally at the junction of the skin with the mucous membrane of the eyelids, nose, mouth, or prepuce. The name was given solely on account of the resemblance to erysipelas, and not because it might be a combination of erysipelas and anthrax; but a mixed infection is more often found in this variety than in the necrotic. The local symptoms besides those of erysipelas are the extensive swelling and the absence of pain. In slight cases there is no redness or vesiculation; when severe there is much redness, with vesiculation and a gangrenous discoloration of the skin.

(*b*) *General.*—So long as the disease is local the constitutional symptoms are slight; when general infection takes place they are the same for both varieties. The severity of the general symptoms bears no relation to the amount of local disease; a small pimple on the neck or chin, without much pain, inflammation, or œdema, may be fatal within three days. On the other hand, an eschar on the temple, with large bullæ above, freely discharging straw-coloured fluid, with swelling all over the head and involving the submaxillary glands, may terminate in recovery. In a few cases with considerable local lesions there are no general manifestations, the patient being able to eat, sleep, and go about as usual; in other cases there is but a slight feeling of illness. In more severe cases the symptoms of general infection set in on the day following the appearance of the pimple; in others they may be deferred for a week or more. The initial symptoms are those of any other febrile disease; such as slight feeling of illness, weakness, chilliness, occasionally a slight rigor, some thirst, at times vomiting, fulness in the head, restlessness, and disturbed sleep. The symptoms afterwards appear according to the internal localisation of the disease, viz. hæmorrhages and gelatinous

exudation in the coats of the stomach and bowels, or in the mesentery and abdominal cellular tissue, with persistent vomiting and diarrhœa; in the lungs, with rapid breathing and a tendency to cyanosis; in the head —meningeal,—with violent delirium, convulsions, and coma; in and about the heart, with rapid collapse and death. During the first few days the pulse may not be affected, but as the state of the patient becomes graver, it will be small, rapid, irregular, weak, and imperceptible. For several days there is usually no fever, and later the temperature rarely exceeds 102° F. In the rectum it is usually 3°-5° higher than in the axilla. It has been noticed to be 104·6° F. in the axilla twelve hours before death. In one case it reached 105·1° in the rectum, and yet recovery followed. In some fatal cases, with lesions in the brain and meninges, the temperature has been from 103° to 106° F. Occasionally the temperature falls before death.

2. **Pulmonary Anthrax—Wool-sorters' Disease.**—The aspect of the disease in this form is really negative. There is no external lesion. There may be no rigors, pain, cough, vomiting, purging, or other distressing manifestations until the near approach of death, and even then the patient may not feel particularly ill. For example, a previously healthy mohair-sorter, aged 46, not feeling very well, called to see his doctor at 10.30 A.M.; during the afternoon, when taking a walk, he noticed his hands were cold (July) and his finger-nails were of a bluish colour. He had a restless night, his breathing being oppressed and rapid, and he died at 10 A.M. Duration, twenty-four hours. A Van mohair-sorter, aged 23, when taken ill, wished to be removed to his parents' home eight miles away. He said he felt "all right." Against the advice of his doctor he went, and died in the cab on the way. Another Van mohair-sorter, aged 39, got up and dressed himself to go to work as usual, but feeling weak he went back to bed, and died at 5.30 P.M. the same day. A strong healthy man, aged 39, after a moderately good night, got up at 6 A.M. to go to work, his hands and feet were cold, he fainted, got into bed again, and died at 2.30 P.M. the same day. An alpaca-sorter, not feeling very well on a Saturday, thought the fresh air at the seaside, 120 miles away, would do him good. On Sunday afternoon he had a short walk in the garden, was worse during the evening, and died early on Monday morning.

Initial.—These, in unmixed cases, are common to many diseases, and are never severe or painful. The patient feels "out of sorts," "not well, not ill," "not half well," "as if he had caught cold and something was coming on." There may be shivering—not amounting to a rigor; in most cases some uneasiness at the chest or stomach, and in all cases great weakness and weariness. The distress, however, is so slight that the doctor is not summoned till one, or more frequently two days have passed, when the patient, without feeling seriously ill, or the friends being apprehensive of danger, may be found in a collapsed condition, cold, almost pulseless, and within a few hours of death.

Alimentary System.—The tongue is always moist and generally coated

with a slight, creamy-coloured covering. Thirst is usual, in a few cases extreme. Appetite is not good, but some have partaken of food moderately after leaving work ill; there may be nausea, weight, and uneasiness at the stomach. Vomiting is mentioned in nearly one-half of the cases; this may occur once only in the early stage of the disease, and is unimportant; in other cases it may be persistent, commencing after the second day, and depending upon concentration of the disease upon the stomach and bowels. Diarrhœa is not so frequent as vomiting; there is occasionally abdominal pain; bloody evacuations have not been noticed.

Respiratory System.—The lungs are always involved, although sometimes the symptoms are slight. In a few cases there is pain in the side, but it is seldom severe or continuous. Nearly all have a feeling of tightness, oppression, weight or pressure about the chest which interferes with the breathing. In some this is the only chest symptom. The breathing is accelerated, difficult, and in the later stage forty to fifty a minute; but in two patients, who were cold and almost pulseless, the respirations were only twenty-five and twenty-six respectively. Cough is generally present, but never severe or very troublesome. In most cases there is no expectoration, in none very much; occasionally it contains numerous small specks of blood, and in a very few, and only in cases which have continued over five days, is it slightly rusty-coloured. The purer the case the less likely is there to be any pneumonia. The breath has often been noticed to have a faint, sickly, peculiar fetid odour. A dusky leaden hue or lividity of face, neck, ears, and fingers, increasing to cyanosis in the collapse stage, is usual.

The percussion note is generally clear; impairment has occasionally been noticed on one side, generally on the right; it is never very decided, even when the examination has been carefully made a few hours before death although much fluid has been found in the pleuræ post mortem. The respiratory murmur on the affected side is feeble during the early stage, and may be inaudible over the upper half or more of the lung at a later stage—the percussion note being clear—from pressure of enlarged glands on the bronchi. Dry, sibilant, cooing sounds are common on the right side; moist, bronchial râles are often present, but crepitations are very rare. The left lung is seldom affected so much as the right, and much less frequently.

The Circulatory Organs.—In some cases the force of the virus appears to fall more upon the heart than on the lungs. Generally the pulse is soft, small, weak, rapid, and irregular, according to the stage of the disease. At the commencement the frequency and force of the pulse may not differ from the normal, so that danger may not be suspected. In the rapid case (see p. 247) the pulse was 100 a minute seven hours before the patient's death; in another case, twelve hours before death, it was only 82. It is, however, usually weak and rapid out of proportion to the apparent severity of the illness (120 to 140), and as the patient approaches the end it becomes very small, irregular, and uncountable. The heart-sounds are also very feeble and at times inaudible.

Nervous System.—In about one-fifth of the cases headache, alone or combined with delirium, has been observed. Coma and convulsions, probably the result of meningeal hæmorrhage, also occur at times. In the majority of cases, however, the mind remains clear throughout the illness.

Skin and Temperature.—The skin is always moist, and in many patients, when the surface of the body is cold, it is bathed with perspiration. The temperature in the axilla in ordinary cases seldom reaches 103 °F.; the few cases in which 104° to 105° have been recorded were prolonged and combined with pneumonia: in one case 107° was noted two hours before death on the seventh day. The temperature is usually 4° to 5° higher in the rectum than in the axilla, and falls as the disease advances.

Urinary System.—The urine is scanty, dark-coloured, and of high specific gravity, even up to 1040. In several cases, both of the cutaneous and pulmonary form, it has been found to contain albumin—in one case as much as "two-thirds"; when present the amount is usually small, but in the majority of cases there is none. In one case of cutaneous anthrax, in which the patient recovered, the specific gravity was 1043, and a quantity of sugar was present.

The symptoms and progress of pure cases are what we may suppose would follow from the inoculation of virulent anthrax virus into the circulating fluids of a healthy person. In the most rapid cases the invading force is so overwhelming that the initial collapse continues, and the strong man yields his life without a sign of resistance. In ordinary cases slight reaction takes place, followed by collapse and death within three or four days, before local inflammatory lesions mask the nature of the illness. In more prolonged cases inflammatory changes take place in the lungs, which very greatly obscure the nature of the illness, and add their own particular dangers, but indicate a diminished risk from the anthrax poison.

Rapid Case.—An alpaca-sorter when at work one morning felt weak and perspired freely. He walked home two and a half miles, and was visited by his doctor at 7 P.M. the same evening. He stated that he had not felt chilly; there had been no thirst, vomiting, or pain; the tongue was moist, slightly coated, and felt cold to the touch; there was some wheezing in the trachea, very little cough, no expectoration; respiration 34, no dulness on percussion of chest, some dry cooing sounds over the right lung posteriorly, no moist sounds; pulse 100, very weak and irregular; temperature in axilla 97·6° F., under tongue 98·1°, within rectum 102·2°. At 11 P.M. temperature—axilla 96·6°, rectum 102·5°; pulse rapid, irregular, uncountable; hands, knees, face, and tongue cold; perspiration free, mind clear. He died three hours afterwards. Duration, seventeen hours.

Ordinary Case.—A sorter of mohair complained of feeling rather sick and weak; he had no pain, slight cough, no expectoration. Chest on percussion in front and behind clear, respiratory murmur over right lung

very feeble, no moist sounds, respiration 24; pulse 126; temperature—axilla 100·4° F. There was nothing apparent in his general condition to cause or correspond with the dangerous character of the pulse. *May 4th.*—In the morning: respiration 28; pulse 120, small, feeble, and uneven; temperature—axilla 98·1° F., mouth 100°, rectum 102·4°. Complained of nothing but sickness, had vomited frequently; at 10 P.M. right lung sounds very feeble, no decided dulness, respiration 30; pulse 116, very weak; temperature—axilla 97·3, mouth 97·9°, rectum 101°; extremities cold. *May 5th.*—Lungs resonant, no crepitations, respiration 40; tongue moist; pulse 120, scarcely countable; collapse increasing; temperature—axilla 97°, mouth 98°, rectum 100·8°. At 5 P.M. the lungs anteriorly were resonant, respiration 48; pulse almost imperceptible; very restless. At 8 P.M. he died. Duration of illness, four days. Anthrax bacilli were afterwards found in the blood.

Prolonged Case.—A Cape mohair-sorter left work on May 19th feeling chilled. He perspired freely, and had slight cough. Temperature 103° F., pulse regular, full, 128. On the 20th had pain in the left side, felt weak, perspired freely, slight rusty expectoration; some crepitations at the base of left lung posteriorly, no marked dulness; temperature 104·2°; pulse 128. On the 22nd passed a restless night; no cough or expectoration. On the 23rd felt better; no pain. On the 24th more pain, particularly in chest. Tubular breathing over lower portion of left lung posteriorly, dulness marked, also slightly on right side; temperature 103·2°, pulse regular, 130. On the 25th felt better; not much pain; mind wandering. On the 26th appeared better; not much cough, some expectoration, not coloured; sat up in bed when doctor was present, and took a pint of mutton-broth. On the 27th much worse, insensible; breathing laboured and rapid; pulse 136, weak and irregular. Hands and arms warm. He died shortly afterwards. Duration, nine days. Characteristic bacilli were found in the pericardial fluid.

3. **Gastro-intestinal Anthrax.**—The symptoms are those of poisoning of a gastro-intestinal character, with or without those of a febrile attack, and develop rapidly into those of general infection as seen in other forms of anthrax. There may or may not be, first, slight febrile symptoms, such as pain in the head, back, and limbs, with nausea, persistent vomiting, abdominal pain, and diarrhœa, which is sometimes hæmorrhagic. The patient feels very weak, helpless, and restless; the pulse is small and rapid; the temperature in the rectum a little above normal; the surface of the skin cold and moist, the respiration rapid, and the face slightly cyanotic; the blood stagnates in the extremities, and occasionally convulsions and coma are followed by collapse and death in from two to five days.

A case fully described by Dr. J. H. Teacher ran its course in 24 hours. The patient was a lead-worker. The most careful inquiry eliminated all readily recognisable sources of infection, and the evidence suggested infection from food or in ordinary deglutition. He was said to have been in perfect health until the morning of January 31st, 1905,

when he rose as usual, but returned to bed on account of giddiness and headache. He did not appear seriously ill until 7 P.M., when he was found out of bed in a restless and excited condition. He was admitted to the Western Infirmary, Glasgow, at 11.15 P.M., in a semi-conscious and delirious state. Respirations were 24 per minute; the pulse was small and wiry, 90 per minute; and the temperature was 98·4 F. There was no sign of disease except tenderness on pressure over the epigastric and umbilical regions. At 3 A.M. on the following day he had a convulsion, beginning in the face, affecting both sides equally, and rapidly becoming general. The urine contained some sugar and albumin. He died at 3.30 A.M., just after the fourth convulsion. (For post-mortem appearances in this case see p. 242.)

Diagnosis.—The occupation of the patient may sometimes afford a clue to the nature of the disease. In the earliest papular stage of the necrotic form, if the patient had been exposed to infection, a pimple on any uncovered part of the body would excite suspicion. The vesicular stage is more characteristic. The exudation may be clear and straw-coloured, or brown. Redness, swelling, and tenderness may extend along the lymphatics to the neighbouring glands. All these signs, however, may be present and yet anthrax be absent. After three days the central early eschar, with surrounding vesicles, redness, extensive œdema, and but slight pain about the part, will be very characteristic. It may be distinguished from a boil or carbuncle by the absence of suppuration, and also by the absence of the moist, yellow, sloughing core; from phlegmonous erysipelas and cellulitis by the absence of pain; and, although these may be attended with vesication and gangrene, the gangrene is more extensive, the vesication is not on the margin of skin surrounding the eschar, and the œdema is not so sharply defined; from chancre by the rapidity of its progress and the more serious constitutional symptoms; from glanders by the absence of the numerous red vesicles and the copious puriform discharge from the nostrils; from malignant œdema—progressive gangrene of the skin—by the absence of crepitation of fetid gas in the cellular tissue, and by cultures and inoculations.

Where there is suspicion of pulmonary or internal anthrax the slightest illness occurring in those exposed to infection should be looked upon as serious, until the possibility of anthrax has been negatived. In the early stage, when the symptoms are the same as those of ordinary ailments, diagnosis is impossible. In the middle stage there is often nothing characteristic in the condition of the patient to determine the grave nature of the disease; hence not infrequently it is unrecognised until the patient is cold, livid, almost pulseless, and dying. In the last stage of rapid or ordinary attacks the combined symptoms, as before given, are sufficiently definite. In the more prolonged cases, complicated with pleurisy and pneumonia, diagnosis is very difficult and uncertain; perhaps a weak pulse and prostration out of proportion to the local lesions may excite a suspicion, which can be confirmed or dispelled by bacteriological methods only.

Bacteriological Diagnosis.—In every case of anthrax an attempt should be made to demonstrate the presence of the bacillus, but failure to isolate the bacillus does not prove absence of the disease. Failure may be accounted for by (1) occurrence of putrefactive changes in the material, (2) insufficiency of the amount sent. Responsibility, therefore, for the diagnosis rests more with the practitioner on clinical grounds than with the bacteriologist. The symptoms of the necrotic variety are in most cases so characteristic as to admit of no doubt. It cannot be too strongly insisted on that recourse must be had to all known bacteriological methods. Careful microscopical examination of fresh or stained coverslip preparations of lymph from the vesicles nearest the eschar, or from under the margin of the eschar itself, frequently, though by no means always, reveals the presence of the bacilli. Later, when putrefactive organisms are present also (and this applies to examination of material taken more than 24 hours after death), the difficulty of identifying the bacillus increases. When verification by both culture on agar or gelatin plates and animal experiment is sought (and this should be done wherever possible), one or the other, if not both, may yield confirmatory evidence. Inoculation of mice or guinea-pigs with suspected material has often proved positive when other methods have failed.

The bacilli are rarely detected in the blood until within a few hours of death in the pulmonary form, or in cutaneous anthrax until after generalisation of the disease. They have, however, been found 48 hours before death. No case of recovery from pulmonary or internal anthrax has been recorded in which the bacilli have been detected in the blood, but recovery in similar circumstances after generalisation of the cutaneous form is not unknown. In addition to that already mentioned, the material most likely to show anthrax bacilli is blood from the heart, spleen, and lungs, pericardial and pleuritic fluid, and fluid from the lateral ventricles. Verification of anthrax bacilli in horse-hair, wool, hides, and skins is difficult, but in several instances their presence has been demonstrated (1, 2, 5, 7, 18, 19, 20, 41). The procedure generally adopted has been to heat an emulsion of the material in physiological salt solution or bouillon for some minutes at 70°-90° C., so as to destroy less resistant organisms, and subsequently to make plate cultures or inoculate susceptible animals. Success has in some cases followed on direct inoculation of dust separated from the material. Differential diagnosis must be made from other capsule-forming, spore-bearing putrefactive bacilli, the bacillus of malignant œdema, *B. anthracoides*, and *B. pseudanthracis*.

Prognosis.—1. *Cutaneous Anthrax.*—The danger to life cannot be estimated by the extent of the local disease. Lesions on the chin and the cheek respectively the size of a split pea, with very slight redness and swelling, have been known to lead to a fatal result within three or four days; yet a larger lesion with extensive œdema and involving the glands may end in complete recovery. The most dangerous sites of the

local lesion are the upper eyelid and neck—the latter on account of its proximity to the larynx and mediastinum. When the lesion is situated on the upper part of the face the exudation may trickle into the mouth, set up vomiting, and increase the danger from secondary intestinal infection. Active reaction with much inflammation around the lesion is generally a favourable sign; but redness may be absent and the patient recover; on the other hand it may be very considerable and the patient die. The prognosis is more favourable with a high than with a subnormal temperature. A falling temperature with an increasing gravity of general symptoms is a precursor of death. Delirium is not uncommon, and is of very serious import, as it generally indicates hæmorrhages between the arachnoid and pia mater.

Vomiting is not of great importance at the outset, but later, if persistent, it indicates general infection. Diarrhœa is rare during the local stage of the disease; afterwards it is occasionally troublesome, and is due to general infection with concentration of the effects of the virus on the digestive tract. Respirations over 40 a minute also indicate localised internal presence of the *Bacillus anthracis*, especially if the cough be troublesome. The pulse is perhaps the best guide to the condition of the patient: so long as it is full and not very rapid the case is hopeful; but when small, feeble, and increasing in rapidity on each visit, it is of serious import. The pulse, temperature, and respiration may, however, be near normal, and the patient not complain of feeling particularly ill, even on the day preceding death.

Duration of Illness.—Number of cases fatal within

2 days.	3 days.	4 days.	5 days.	6 days.	7 days.	8 days.	9 days.	Over 9 days.	
3	7	23	11	13	12	6	6	2	—Total 83

2. *Pulmonary Anthrax.*—When a strong man employed on dangerous wools complains of slight illness, as if he had got a cold, and after careful examination nothing more is apparent, a guarded prognosis must be given; he may be dead within twenty-four hours.

If the onset be more decided, and there has been shivering, followed by other symptoms of a "severe cold," and a temperature above 102·5° F., the prognosis will be more favourable; these symptoms indicate that the patient has been able to resist the onslaught of the specific disease; and, although bronchopneumonia, pleuritic effusions, and secondary suppurations may follow and add their own dangers, these complications are antagonistic to anthrax development, and the chances of the patient's recovery are more favourable. In the absence of bacteriological proof of the presence of the bacilli in any case of recovery from pulmonary anthrax, no definite statement as to the number which recover is possible. But several cases of recovery have been seen in the Bradford district in which the symptoms suggested strongly this form of the disease.

Duration of Illness.—Number of cases fatal within

1 day.	2 days.	3 days.	4 days.	5 days.	6 days.	7 days.	10 days.	Over 10 days.	
5	22	21	16	7	3	3	3	2	—Total 82

Mortality.—In Europe about 25 per cent of all cases prove fatal. Thus in Great Britain of 320 reported cases (1899-1905) 85 were fatal —26·6 per cent. Of these 13 were of the internal variety, and were all fatal. Excluding them the proportion of deaths to attacks in the cutaneous form was 23·4 per cent. In Italy, in the eleven years (1880-1890), of 24,052 cases 5812 were fatal, or 24·1 per cent. W. Koch (1886) noted 422 out of 1473 published cases of cutaneous anthrax as fatal—32 per cent. In the outbreaks of pulmonary anthrax among rag-sorters in Lower Austria (1870-1886) the mortality was 88·6 per cent. It is universally agreed that neglect of early treatment in the cutaneous form of the disease is one cause of the high death-rate. Thus for a number of years the fatality of cases treated in hospitals may be considerably less than that stated. At Guy's Hospital, for instance, between 1896 and 1904, of 56 cases treated 4 only proved fatal—7·1 per cent. The mortality varies greatly according to the variety of the disease and other conditions. What determines the form assumed—whether it be differing degree of virulence of the bacillus, or differing degree of resistance in the human subject—is unknown.

Treatment.—From the earliest times all writers on the treatment of anthrax have recommended the destruction of the primary focus of infection by caustics or cauteries. The actual cautery is still the chief treatment in many parts of Russia, Siberia, Persia, and other countries of Asia where the disease is most prevalent. In England surgical interference usually takes the form in cutaneous anthrax of free excision, and swabbing the wound with pure carbolic acid. At Guy's Hospital, in addition, powdered ipecacuanha is commonly dusted on the wound, and ipecacuanha in ten-grain doses is given internally. Davies-Colley was guided in introducing this treatment by the experience of Muskett in South Africa, who regarded ipecacuanha as a specific for anthrax, and by this means alone had treated fifty cases without fatal issue. Washbourn found, too, that ipecacuanha destroyed anthrax bacilli, but not spores, which are not formed in the body. Five per cent carbolic acid is often injected into the subcutaneous tissue around the margins of the lesion in several places, either in addition to or instead of excision.

In pulmonary anthrax the progress of the disease is generally so rapid that, almost before a diagnosis can be made, recovery may be out of the question. In the previous edition hope was expressed that a serum from some artificially immunised animal might be discovered which would have some arresting action on the progress of the disease if given after infection by anthrax virus. And in this connexion it was suggested that use of the serum of a naturally immune animal—as the Algerian sheep—might be tried by subcutaneous or intravenous injection. Since this was written progress in serum treatment, both in the cases of man and farm animals, has been considerable.

Production of passive immunity and recognition of specific protective substances against anthrax bacilli in the blood-serum of animals brought to a high degree of active immunity was made about the same time, and

independently, in 1895 by Sclavo in sheep, and by Marchoux in both sheep and rabbits. Later Sclavo instituted experiments as to the relative strength in immunising effect of the serum of various animals—the sheep, goat, ox, horse, and the ass—and found that of the ass the most powerful. To produce active immunity both these investigators used the vaccins of Pasteur, and subsequently injected cultures of virulent anthrax bacilli subcutaneously in gradually increasing doses. To obtain anthrax serum more quickly than this method allows of, Sclavo evolved the combined active and passive immunising methods, with which he still obtains the best results, namely, injection of 5, 10, or 15 c.c. of the serum of an immunised animal, together with a culture of slightly attenuated anthrax bacilli, followed at fortnightly intervals later by subcutaneous injection of virulent cultures in increasing doses over a period of several months. Having satisfied himself of the curative effect of the serum when administered to sheep twenty-four hours after inoculation of virulent anthrax cultures, and of its innocuousness alone in large doses, Sclavo began to treat cutaneous anthrax in man by its means in July 1897. The serum, after ether has been added to the extent of 3 per cent of the whole bulk, is put up in tubes containing 10 c.c. Sclavo directs that 30 or preferably 40 c.c. should be injected into the abdominal wall (10 c.c. in four different places) as the initial dose. On the following day, if there is no improvement either in the local or general symptoms, 30 or 40 c.c. should again be injected in the same manner. Where the symptoms are very grave 10 c.c. may with advantage (in addition to the abdominal injections) be injected intravenously, preferably into one of the superficial veins on the back of the hand, and repeated later if necessary. A rise of temperature following the injection is to be regarded as a favourable sign.

The serum, if kept cool and in a dark place, remains fully active for at least two years. Sclavo would rely on the use of his serum alone, and deprecates all surgical interference. In England the inclination has decidedly been to employ it in all cases in the doses recommended by him, but, in addition, to excise or inject 5 per cent carbolic acid round the local lesion.

Sclavo (1903) refers to 164 cases of cutaneous anthrax treated by his serum in Italy. Among these there were ten deaths, 6·09 per cent, as compared with a mortality of 24·1 per cent for all cases in Italy. One of us (T. M. L.) has published details of sixty-seven of these cases, in fifty-six of which serum alone was used. Excluding one fatal case and two in which there was loss of tissue, the duration of illness from commencement of treatment to recovery appears not to have been more than fourteen days in any of the fifty-three cases, and in forty-four of them the average duration was eight days. In many the resulting scar is described as insignificant. Anthrax bacilli were found in the blood and urine of two cases which recovered. There was no case of the pulmonary or gastro-intestinal variety. So far in the few cases of this form in Bradford treated with serum, one case (in which the symptoms pointed strongly

to internal anthrax, although bacteriological proof could not be obtained) recovered after injection of 200 c.c.

Mendez of Buenos Ayres (1904) refers to 1073 cases treated with serum from the horse, immunised by him in the same way as was done at first by Marchoux and Sclavo, with forty-four deaths—4·19 per cent. It is not stated whether the serum treatment was used alone or combined with operative treatment. Since 1903 the dose recommended by him is only 3 c.c. The diminution in temperature, pulse, and respirations, following on injection of the serum, is as rapid and marked, he states, as is that which occurs after the crisis in pneumonia. His communication does not suggest that the disease is of a milder type in Argentina than it is in Europe.

Sobernheim (43) confirmed the main results obtained by Sclavo and Marchoux,—presence of specific protective substances in the serum of highly immunised sheep,—and proved that sheep could be immunised with certainty against anthrax by the specific serum; later (1900-1902) he developed the combined active and passive immunising method on such practical lines that it has in some measure replaced that of Pasteur. The advantages, according to his statement, are that this method (1) is effective in one day, and need not be repeated; (2) confers probably a more lasting protection, as a stronger dose and more active cultures are used than is the case with Pasteur's vaccin; (3) protects from infection by way of the intestinal tract; and (4) can be used for curative purposes. The number of animals thus treated (March 1904) was about 75,000 in Europe and South America, with nine deaths attributable to the inoculation.

The efficacy of anthrax serum cannot be tested in the same way or with the same exactitude as antitoxic serums. Recourse must be had to animal experiment—intravenous injection of 1-6 c.c. of the serum into six rabbits, and subcutaneous inoculation shortly after of virulent anthrax culture in known small amounts. Survival of one-half of the animals and prolongation of life of the remainder for a longer period than that of the control animals, would point to a serum of high protective power.

The most contradictory views have been expressed as to the way in which the serum acts. Metchnikoff, Marchoux, and others attribute the immunity produced to phagocytosis, the action of which, however, is dependent on the degree of virulence of the bacilli. Sclavo considers that the bactericidal substances present in the serum are of less importance than the effect upon the phagocytes themselves, the serum promoting the phagocytosis of the bacilli (stimulins). On the other hand, the researches of Sir A. E. Wright and Capt. Douglas on the opsonic power of human serum towards the anthrax bacillus shew that under the influence of normal serum the phagocytes englobe the bacilli, but that this effect is not produced if the serum be first heated to 55° C. for half an hour. It is possible, therefore, that this opsonic power may be raised by the high opsonic content of the serum. Recently Cler, using the white blood-corpuscles of a guinea-pig and adopting

the methods of Sir A. E. Wright and Capt. Douglas, found that anthrax bacilli, sensitised by the action of inactivated anthrax immune serum, were englobed by phagocytes, phagocytosis commencing in 15 minutes and being complete in from 1 to 2 hours. The successive stages of the phenomenon are illustrated in his paper. When physiological salt solution was used instead of the inactivated serum only a feeble reaction took place, as occurred also when the white corpuscles were sensitised by the inactivated serum, washed from adhering serum, and mixed with an emulsion of unsensitised anthrax bacilli. Cler considers, therefore, that the anthrax serum contains an antibody (*substance sensibilisatrice*) which links the alexin to the bacillus, furthering positive chemiotaxis. Sobernheim (45), while recognising that bactericidal action of the anthrax serum has not been certainly proved either within or without the body, inclines strongly to the view that the artificially acquired immunity is to be referred to bactericidal influences, inasmuch as anthrax infection is mainly septicæmic. Anthrax serum and normal serum of the same species of animal shew no difference in their action on anthrax bacilli *in vitro*, nor is apparent change brought about in their morphological appearance. Anthrax bacilli, he says, can be shewn to be present microscopically and by culture in the exudation several days after inoculation of sheep which have been immunised to such a degree as to survive enormous doses of virulent anthrax.

Although the anthrax-poison is not comparable with that of diphtheria or tetanus (no toxin having yet been obtained from filtered cultures, injection of which produces the specific effects of the disease), the manifestations of anthrax in the human body undoubtedly suggest production of a toxin of some sort. The local necrosis, with excessive leucocytosis around the œdema, the effects extending to distant organs, the constitutional symptoms, and the poverty of the blood in bacilli until immediately before death, are inconsistent with the view that the symptoms are due to the multiplication of the bacilli apart from toxic production. The accounts of rapid improvement following on injection of serum in the human subject in many cases would be most easily explained on the supposition of the presence of antitoxic substances. It is on this account that Mendez describes his serum as "anthrax antitoxin."

Preventive Measures.—Regulations under section 79 of the Factory and Workshop Act, 1901, now apply in premises where the sorting and combing of specially dangerous classes of wool are carried on (Van mohair, mohair, so-called Persian, alpaca, Cashmere, and camel hair). The main safeguard required is localised exhaust ventilation in a downward direction by means of a fan at the perforated tables on which opening of the bales and sorting of the wool are done. Exhaust ventilation must be applied also in connexion with dust-extracting apparatus. Other necessary provisions are:—(1) the burning of the dust so collected; (2) washing accommodation, cloak-room, and meal-room; (3)

exclusion of persons with uncovered cuts or sores; (4) requisites for treating scratches, etc; (5) cleanliness of work-rooms and destruction or disinfection of clippings of dead skin; and (6) exhibition of a notice describing the symptoms and pointing out the necessity for prompt treatment. In warehouses and tan-yards where dry hides and skins imported from China and the West Coast of India are manipulated provisions (2) to (6) apply in modified form. It would be well were they adopted in all premises where wools, hairs, hides, horns, etc. of foreign origin arrive.

Disinfection of dangerous wool by steam has been considered impracticable hitherto, and certainly high pressures, such as are commonly used in disinfecting apparatus in this country, would damage the material for manufacturing purposes, except, perhaps, in the case of Persian wool, which is of a brown colour. No doubt the immense quantity of wool to be dealt with has so far prevented thorough inquiry on this point, although in the melange printing process, in order to obtain certain effects, mohair is submitted to steam at 5 lbs. pressure for twelve hours without detriment. Immersion of suspected material in water at a temperature of 210° F. would greatly diminish the risk in subsequent processes.

After thorough investigation in the Imperial Health Office of Berlin, disinfection by steam, under prescribed conditions, or simple boiling, has been accepted as practicable in the case of horse-hair and bristles (except when white or light-grey in colour). If, in addition, overalls and gloves are worn by those who prepare the hair for disinfection, risk is very slight. Success with steam disinfection is, however, only to be secured by minute care in detail—construction and regulation of the apparatus so that the current saturated steam in contact with the material is maintained under a pressure of 1·15 atmospheres (17 lbs.), equivalent to a temperature of 106° C. (220° F.), for one half-hour.

Chemical disinfectants have not as yet been applied successfully in the industrial use of wool, horse-hair, or hides and skins. There is no legal power to prevent importation of infected material, and from the Persian Gulf much wool is received in what is known as a "false-packed" condition, *i.e.* containing inferior and dangerous material concealed in the fleeces. Manufacturers would wish to have pressure brought to bear on the consignees of material at the place of shipment, so as to compel them to keep separate the inferior and "fallen fleeces" from the sound. A still more effective pressure would be refusal on the part of the manufacturers to purchase wool from shipping agents in ports where "false packing" is practised.

Probably inclusion of anthrax as one of the industrial diseases to which the Workmen's Compensation Act applies, will lead to greater care in buying, and stimulate inquiry as to more effectual precautions than are now taken.

In view of the greatly increased mortality in cases in which treatment is delayed, active steps should be taken to report illness, whatever may be its nature, among persons who have been exposed to possible anthrax

infection; further, the patient should be visited by a medical man specially appointed for this work, who should, except when anthrax can be positively excluded, recommend or give a full dose of antianthrax serum.

The ease with which material for bacteriological diagnosis can be obtained without opening the body in suspected cases of death from anthrax, appears to us to make it unnecessary now to carry out a full examination of the viscera in all cases, unless means are taken to sterilise the blood and so forth before they enter the drain.

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INFECTIVE DISEASES OF CHRONIC COURSE

TUBERCULOSIS

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Tuberculosis is an infective disease, produced by the *Bacillus tuberculosis.* It occurs as a natural disease in human beings, in some of the domesticated animals, and in many wild animals when kept in captivity. A form of the disease is met with even in cold-blooded animals (fish, blindworm, turtle). Tuberculosis is widely prevalent in the human race and in cattle. One-seventh of mankind are said to die of tuberculosis, but in this country the proportion is not now so high. Thus, during the decade 1891-1900, of a total of 5,575,375 deaths throughout England and Wales, 616,006 were due to tuberculosis —almost exactly 1 in 9; while for the previous decade the figures were 5,244,771 and 589,390 respectively, a ratio of 1 in 8·7. The mortality from tuberculosis has declined greatly during the last half-century, and still exhibits a steady decrease. [For further details see Vol. I. p. 48.] The prevalence in cattle may be stated as varying from 10 to 20 per cent of all cows.

Bacillus Tuberculosis (Koch, 1882).—In nature, so far as is known, the bacillus which is the cause of tuberculosis grows only in the bodies of animals affected by the disease. Outside the body it can be cultivated in specially prepared media, but it does not occur naturally in any particular soil or medium. It consists of slender rods, varying in length between 1·5 and 3·5 μ. They are often bent, and when long may present a beaded appearance. This beaded appearance is due to the presence of clear areas in the rod, which were at first considered by Koch to be spores. There is, however, no evidence that the bacillus forms spores; and it is improbable that it does so. In certain circumstances the bacilli may grow into much longer threads which exhibit true branching. The organism is therefore to be regarded botanically as a streptothrix (see p. 302). Irregular involution-forms also occur. Certain oval bodies, known as Schrön's capsules or Cornet's spores, which are found in chronic caseous foci, appear to represent degenerated bacilli.

Reaction to Stains.—The bacillus behaves in a characteristic manner to some of the aniline dyes. It takes up the stain of fuchsin and of gentian violet when these are dissolved in an alkaline liquid, or in one containing carbolic acid or aniline; and the colour is not removed by mineral acids up to 25 per cent strength or by alcohol. The most convenient method of staining tubercle bacilli, whether in the sputum or in tissues, is to use a solution of fuchsin dissolved in carbolic acid, as follows:—Fuchsin 1 gramme, alcohol 10 c.c., 5 per cent solution of carbolic acid up to 100 c.c. A preparation of sputum may be stained for five minutes to a quarter of an hour in this solution, which is warmed till the steam rises, and is then placed in a 25 per cent solution of sulphuric acid until it is decolorised. As a rule this takes a minute or two, but no harm comes to the preparation if it be left a quarter of an hour in the acid. It is then well washed in distilled water, to get rid of the excess of acid, and as a rule it takes on a faint pink tinge. It must now be counter-stained, preferably by a dilute solution (1 to 2 per cent) of methylene blue. Half to one minute is sufficient for this, and after washing in water, the preparation is ready to be mounted. For sections of tissues it is best to stain for fifteen minutes in the warm fuchsin solution, after sticking the preparation on the cover-glass or slide. After counter-staining with methylene blue the section is to be dried with fine filter-paper, washed rapidly with alcohol, clarified with xylol, and mounted in xylol-balsam. By this method the tubercle bacilli are stained red, most other organisms which may be present being decolorised by the acid. These, as well as the ground-tissue and cells, are stained blue by the methylene blue. It is now known that the staining reaction formerly regarded as characteristic of the *B. tuberculosis* is manifested, more or less exactly, by a considerable number of organisms. Of these the most important are (1) the leprosy bacillus; (2) the smegma bacillus, which occurs on the external genitals; and (3) bacilli which grow saprophytically on various grasses (Timothy bacillus, grass bacillus), and others which are found in milk, in butter, and in the dung of cattle. Certain forms of streptothrix, found in rare pathological conditions, are also "acid-fast" (säurefest). Indeed, some thirty different organisms, all of which behave like the tubercle bacillus in regard to aniline dyes, have been described by various writers (Abbott and Gildersleeve).

Gentian violet may be used as a stain for the tubercle bacillus, the specimen being fixed with iodine solution and decolorised with alcohol (Gram's method); bismarck-brown, eosin, or vesuvin may be used as a counter-stain. This method gives very good results; but the other (Ehrlich's method) is more generally serviceable.

Cultivation of the Bacillus.—The *Bacillus tuberculosis* grows best at the temperature of the body. At low and high temperatures its growth is impeded or completely stopped. The range of temperature at which it will grow is between 28° and 42° C. It may be artificially cultivated by using various media. Solidified blood-serum is the best for obtaining the bacillus from the tissues, and was the one used by Koch in his

first research. When the surface of the solidified blood-serum is inoculated with pure tuberculous material, and the tubes are kept at a temperature of 38° C., no growth appears as a rule during the first week, but after 7 to 10 days white specks are seen on the surface of the serum, which appear as dry flakes under the microscope. The growth extends in a circular manner from these foci; and the older growths, while still remaining dry, become crinkled and folded, presenting a very characteristic appearance. The growth is very slow, and it may be weeks before it covers a large area of surface.

The bacillus may also be grown on other solid media, such as blood-serum containing gelatin, or peptone-agar containing 4 to 8 per cent of glycerin. On peptone-agar without glycerin the bacillus does not grow. Glycerin not only aids the growth in solid media, but, in the percentage mentioned, stimulates the bacillus to grow in liquid media, such as peptone-bouillon. It can also be grown on potato in sealed tubes (Pawlowsky). Grown on solid media the bacillus is apt to lose its virulence. In liquid media containing glycerin the virulence may be maintained somewhat longer.

The action of direct sunlight is fatal to the bacillus. This was first shewn by Koch, and has been confirmed by subsequent observations. Oxygen is necessary for the growth of the bacillus.

Agglutination.—Tubercle bacilli are agglutinated into clumps by the action of serum taken from a patient suffering from tuberculosis. This reaction, however, is not invariable, and may be exhibited at times with serum taken from healthy persons.

Chemical Products.—But little is known of the chemical bodies which are produced by the *Bacillus tuberculosis* in its growth. Koch separated a substance called "tuberculin," which has a specific action. It is prepared by growing the bacilli for six to eight weeks in a slightly alkaline veal-broth, containing 1 per cent of peptone and 4 to 5 per cent of glycerin. After cultivation the liquid is evaporated to a tenth of its bulk and filtered through porcelain; this filtrate is the liquid which is called tuberculin, or "old tuberculin," to distinguish it from more recent preparations similarly named; it contains 40 to 50 per cent of glycerin, which keeps it aseptic. By adding alcohol the active principle is precipitated in an impure state. This differs from most other bacterial products in resisting a high temperature, even the boiling-point of water. The specific action of tuberculin is shewn by its producing a great rise of temperature in men and animals infected with tuberculosis, while similar small doses injected into healthy individuals produce no rise of temperature. The fever ensues from 6 to 12 hours after the injection, and lasts a varying time—in some cases 24 hours, in others 48, or even longer. Large doses may produce in a tuberculous individual or animal great bodily depression, leading to collapse. Dr. W. Hunter shewed that tuberculin contained albumoses, which are probably the cause of the febrile symptoms. The essential toxin is probably not of a proteid nature, as it appears to be formed in non-proteid media

and resists a temperature at which most albuminous bodies are coagulated.

Of the chemical products to which the bacillus gives rise in the body practically nothing is known. There may be a substance or substances causing caseation, and there must be a chemical body which produces the fever. These, however, have not been satisfactorily isolated. Prudden and others found that, when injected into an animal, the dead bacilli produced local inflammation and hyperplasia, which ended in fibrosis without further spread of the disease. Apparently the dead bacilli contain within them poisonous materials (intracellular toxins) capable of exciting inflammation, whereas they are necessarily incapable of multiplication within the body. Drs. Bulloch and Macleod found that the bacilli contained a fatty substance, and also a form of wax, the latter being responsible for the peculiar staining properties of the organism. The fat is said to be toxic (Sciallero). Ethereal extracts of the bacilli exert a necrotic action, whereas chloroform extracts lead to fibrosis; to the former Auclair assigns the property of causing pulmonary consolidation, while Armand-Delille has shewn that it can produce characteristic granulomas. On the other hand, the bodies of the bacilli, when deprived of fat, are still toxic (Cantacuzène).

Koch's "new tuberculin" (TR) is prepared by grinding up cultures of the bacilli with distilled water. The first quantity of the resulting fluid is decanted and constitutes "oberer tuberculin" (TO). Fresh amounts of water are added and the trituration repeated until no solid residue remains, this solution of the organisms constituting the new tuberculin.

Avian Tuberculosis.—Tuberculosis is found as a natural disease in fowls, pheasants, pigeons, turkeys, peacocks, and other birds which are kept in captivity. The bacillus, which has been separated from the lesions produced, differs in some respects from that found in cattle and in human beings. It is stained in the same manner by fuchsin, and may be grown in the same media as the human and bovine strains of the *Bacillus tuberculosis*; but it differs in that it is more vigorous and resistant.

This bacillus grows luxuriantly at a temperature of 43° C., at which the human and bovine *Bacillus tuberculosis* will not grow—a feature corresponding apparently with the much higher body-temperature of birds. The appearance of the cultures is also different; instead of being dry and crinkled they are moist and soft. The results of inoculation also differ: in guinea-pigs and rabbits the inoculation of the human bacillus produces a spreading disease, which eventually invades most of the organs of the body, whereas the bacillus of avian tuberculosis produces in the guinea-pig a local disease which does not spread to the internal organs. Dogs are immune to avian tuberculosis, but they can be infected by large doses of human and bovine bacilli; on the other hand, the hen usually cannot be infected with human or with bovine tuberculosis. Although from these statements it would appear that avian tuberculosis is not the same disease as bovine or human tuberculosis, yet there are some facts which shew that it is a modified form of that

disease. Thus, it has been shewn that inoculation of human tuberculosis into fowls sometimes succeeds, and when it does, reinoculation is also successful. Instances of infection of hens resulting from the ingestion of human sputum are also recorded. Moreover, when a slight lesion is produced in guinea-pigs by the inoculation of avian tuberculous material, the transmission from guinea-pig to guinea-pig results in the characteristic spreading disease which is observed after the inoculation of human tuberculosis (Nocard). This, perhaps, is even more evident in rabbits than in guinea-pigs.

Bovine and Human Tuberculosis.—Much controversy has raged round the question of the identity or diversity of the organisms which produce disease in mankind and in bovine animals respectively, since Koch's pronouncement (1901) that human tuberculosis cannot be transmitted to cattle and that bovine disease is not dangerous to man. The bacilli separated from tuberculous lesions in man, in cows and pigs, and in all other domesticated animals except birds, are practically indistinguishable. They have the same appearance microscopically; they react in a similar manner to stains; in artificial cultivation they grow in a similar manner, and when inoculated into animals the disease produced is in all cases alike both anatomically and in its mode of distribution. There are indeed some differences in the manner in which tuberculosis affects the human being and affects the cow; but no absolute distinction exists. Thus in cattle the bacilli are found present in closely packed masses, and tuberculosis of serous membranes assumes the peculiar shape of pedunculated nodules ("grapes"). Similar formations are occasionally met with in mankind (Besse, MacCallum); while in children masses of bacilli, resembling those seen in bovine tubercle, may sometimes be found in tuberculous lesions. It has now been proved by the experiments of many observers that cattle can be infected with bacilli derived from human sputum. The converse experiment of inoculating human beings with bovine tubercle cannot be legitimately tried, but instances of accidental inoculation in veterinary surgeons and butchers are not very rare, and some writers maintain that tuberculosis in infants and young children is mainly due to infection derived from milk (Behring, Raw).

On the whole it seems probable that all forms of tuberculosis, in man and animals, are produced by the same organism, modified by the special environment in which it exists in different hosts. All pathogenetic varieties give rise to the same product, tuberculin, and inoculation with one form appears to confer some degree of immunity against the others. The relationship between the pathogenetic form and the other acid-fast bacilli is uncertain, but is probably close. The latter may be provisionally regarded as different species of the same genus, whereas the different pathogenetic organisms seem to be varieties of the same species.

Lesions produced by the Bacillus Tuberculosis.—Wherever the *Bacillus tuberculosis* grows in the animal body it produces a lesion which has certain definite characteristics; and it is necessary to study this lesion before we consider the distribution of the disease in individual

cases, or its mode of extension. The lesion consists of small whitish nodules, which may be more or less numerous, and by their aggregation may form large masses. Each of the small primary lesions is called a granuloma or a miliary tubercle. Either singly or fused into masses they undergo retrogressive changes by which their original structure is completely lost; the chief of these is caseation, fatty degeneration or necrosis of the cells forming the tubercle. The caseated matter may soften and be discharged, or it may calcify. The second change which occurs in the tubercle is fibrosis; it is frequently associated with pigmentation. The primary lesion, the grey granuloma, is composed of cells, and throughout its whole extent is non-vascular—a point of some importance in the explanation of the degenerative changes which occur.

Microscopical Appearances.—According to the size of the cells which compose the grey granuloma, a small-celled and a large-celled tuberculous nodule may be distinguished. The small-celled granuloma consists of mononuclear cells, derived from the leucocytes of the blood and lymph. The large-celled tubercle consists in the main of so-called epithelioid cells—cells which have a definite outline, are roughly ovoid, and are often compressed. These cells, especially in the early stages of the formation of the tuberculous nodule, frequently shew the phenomenon of karyokinesis, that is, a division of their nucleus with a star-shaped figure at each end. This change is also observed in the endothelial cells of the blood-vessels. Giant-cells are present both in small-celled and large-celled tubercle; they vary in size, and present the common characteristic of a large number of nuclei at the periphery. The nuclei are oval, and usually are not distributed evenly round the periphery of the cell. In most cases they are collected to one side, and they are not infrequently two rows deep. Between the epithelioid cells there is sometimes a fine reticulum, as in lymphoid tissue, and there is a serous or fibrinous exudation from the blood-vessels. The number of small cells present in the tuberculous nodule varies; and, according to Baumgarten, the migration of leucocytes occurs earliest when there has been an injury to the tissue. They collect round the periphery of the tubercle. Baumgarten considers (and his opinion has been accepted by most pathologists, including the German school) that the first change in the formation of the grey granuloma is the proliferation of the fixed tissue-cells, to form the so-called epithelioid cells; and that the migration of leucocytes is a subsidiary phenomenon, occurring at a later period. This view is combated by Metchnikoff, who considers that the tuberculous nodule "is composed of a collection of phagocytes, mesodermic in origin, which move towards the spot where the bacilli are situated, and englobe them." Thus, in the liver, if the tuberculous nodule be examined shortly after its formation in experimental tuberculosis, it is found that the epithelioid and giant-cells are formed by the large mononuclear leucocytes and cells derived from the vascular endothelium, and that the hepatic cells take no part in the formation of the tubercle. He makes a similar statement with regard to the lungs. The leucocytes present in the tuberculous nodule

are almost all mononuclear. Polymorphonuclear leucocytes are present, and take into their substance tubercle bacilli, but they soon die, being eaten by the mononuclear phagocytes (macrophages). These macrophages can destroy the tubercle bacilli.

Retrogressive Changes of the Tuberculous Lesion.—*Caseation.*—The first and chief retrogressive change which occurs is caseation; as the tubercle is a non-vascular collection of cells, and is prone to unite with similar tubercles in the neighbourhood, thus forming a large non-vascular mass, death of the parts farthest removed from the blood-vessels would be likely to occur, as in an infarct, where the blood-supply to a portion of the tissue has been cut off by blocking of the artery supplying it. It is, however, more probable that caseation is a specific action of the *Bacillus tuberculosis* itself. Apparently a chemical substance is secreted by the bacillus which kills the cells; in any case it is certain that many of the cells containing tubercle bacilli die and become completely degenerated. This is seen even in very small miliary granulomas. According to Baumgarten, the death of the leucocytes occurs first, and then that of the epithelioid cells; while the giant-cells are themselves in a state of defective vitality, so that they do not undergo division into daughter-cells, as the presence of numerous nuclei in their substance would suggest. The central parts of these cells often die first, and it has been suggested that the nuclei take up a position at the periphery as being the zone where nutriment is most plentiful.

Microscopical examination shews very various appearances. In the early stages of the death of the cell the protoplasm becomes granular and fatty, and finally breaks down; the nuclei lose their oval form, becoming shrivelled and broken up into irregular masses, which even a long time after the cell has disappeared take up the stains of logwood and methylene blue. Where a number of cells of the tubercle have undergone caseation, forming a mass of perhaps a quarter of an inch in diameter, no structure is apparent in the centre of the caseated area; a few darkly stained spots represent, perhaps, the remains of the nuclei, and the fine granules are chiefly fatty matter. Towards the periphery of the caseated patch, however, nuclei are seen, which present a shrivelled appearance, and are beginning to break up into small particles. Around the caseated area the appearances vary according to the stage of the tuberculosis. There is more or less fibrosis, with infiltration by leucocytes; and there may be outlying tuberculous nodules which present the appearances previously described. The caseated nodules by joining together produce large tuberculous masses, especially in bovine tuberculosis. The softening of the caseated matter, and its expulsion through the bronchial tubes, may result in the formation of a cavity in the lungs; a similar process may give rise to an ulcer on a mucous membrane, or to a tuberculous abscess or fistula in other parts.

Calcification is a retrograde change in the tubercle which occurs after caseation. The actual deposition of the phosphate of lime, which is the chief component of the calcareous matter, has been attributed to the

diminution in the amount of carbonic acid at the spot where it occurs. It is observed in old tuberculous lesions in man, cattle, and pigs, but not in guinea-pigs or in rabbits, and very rarely in the horse. It occurs, therefore, in animals in which tuberculosis may take a very chronic course. It is difficult to state the earliest period at which calcification may occur, but in experimental tuberculosis in the pig it has been observed as early as 106 days after infection.

Microscopically, calcareous matter is seen deposited in the form of granules in the cells. It is, however, not infrequently in the form of a nodule, which by treatment with acid shews concentric rings, as in a renal calculus (Schüppel). In experimental tuberculosis in the Algerian rat (*Meriones*), an animal which is very refractory to the disease, Metchnikoff found bodies similar to those described by Schüppel as occurring in human tuberculosis, and observed their mode of formation in various specimens. They are, in short, the results of the degeneration of the tubercle bacillus in the interior of the giant-cell. In the course of the disease, which is extremely slow in its progress, the bacilli become surrounded within the cell by concentric layers of an amorphous, colourless substance, which eventually becomes impregnated with phosphate of lime. The concentric membranes are not affected by alkalis, and do not give a red colour with Millon's reagent; but they are dissolved by concentrated acids. They appear to be composed of a substance similar to that enveloping the tubercle bacillus. The bacillus inside the concentric layers degenerates, so that although at first it takes the stain of fuchsin or gentian violet, in the later stages it does this very imperfectly, and finally not at all. These observations appear to shew that the concentric bodies are really part of the products of the fight between the bacillus and the giant-cell.

Calcification is one of the modes by which tubercle heals, as the completely calcified lesion is no longer infective. It does not differ essentially from the calcification which affects foreign bodies (parasites) or other degenerated tissue, such as atheromatous arteries or old uterine myomas.

Fibrosis is a second mode of healing of the tuberculous nodule. It occurs at the periphery of the nodule, and is the result of the inflammation set up by the presence of the grey granuloma. It occurs in chronic tuberculosis, and is very evident in cases where the tissue has been injured. Thus, in the local lesion following the injection of tuberculous material under the skin, fibrosis is extensively produced; also in parts which are exposed to friction, as in joints, when they are infected by tuberculosis. *Pigmentation* frequently accompanies fibrosis, and is due to hæmoglobin derived from blood-corpuscles which have escaped from the congested blood-vessels. It may occur around the miliary granulomas, when these have been surrounded by a zone of congestion. Thus, in the peritoneum and lung it is not infrequently observed that a small grey granuloma is surrounded by a bluish ring of pigment and by fibrous tissue.

Lesions of various Parts as they occur in Tuberculosis.—The

tuberculous lesion has the structure just described, in whatever part of the body it may be found; but the appearances vary according to the arrangement of the primary lesions, to the degree of the degenerative changes present, and also to the presence or absence of coincident non-tuberculous changes.

The Lungs and Pleuræ.—In the lungs tuberculosis may occur either in the acute or caseous miliary form, in the chronic form, or in a form in which fibrosis is the chief element.

(*a*) *Acute Miliary Tuberculosis.*—This is secondary to a primary focus elsewhere in the body. The naked-eye appearances are those of miliary granulomas scattered more or less uniformly throughout the substance of the lung. Some of the granulomas may shew central caseation. The lung-tissue itself is generally congested, and there may be distinct zones of congestion round the tuberculous nodules, especially when beneath the pleura. Patches of collapse and emphysema are also frequently observed.

A slightly less acute process in which the tubercles are large and apt to blend together into masses—" racemose patches"—may be called *acute caseous tuberculosis*, and forms a connecting link with the next variety.

(*b*) *Chronic Pulmonary Tuberculosis.*—The most advanced stage of the disease is at the apex of the lung, and here is found a cavity, or a series of cavities, varying in size and shape, and surrounded by pigmented fibrous tissue, shewing the chronic character of the lesion. In very old cavities the wall is smooth, but in more recent (although still chronic) examples the walls may be lined by a cheesy material, and numerous cavities may be joined together, forming sinuous tracks in the upper part of the lung. Below the cavity, in the upper lobes and to a varying extent in the lower, the more recent deposits of tubercle are seen, consisting either of miliary granulomas, uniting into racemose patches and commencing to degenerate, or of quite recent cavities, full of a soft, yellowish, cheesy material formed by the complete degeneration of the racemose patch. The racemose patches are not only in the substance of the lung, but near the surface, on which they may form slight projections; on section they may be wedge-shaped like an infarct, shewing that they were formed either by infection through a terminal artery or by inhalation through a bronchial tube. Both lungs may be affected, and the extent of the recent tuberculosis is usually greater in the lung which was first affected than in the other. In this form of tuberculosis, therefore, there are evidences of a chronic lesion which has lasted a long time—it may be years—with a subsequent acute outbreak of tuberculosis below the chronic lesion; such acute extensions are constantly occurring during life, and in one of these death may ensue. The bronchial glands also are usually affected by tuberculosis in the manner presently to be described.

The process appears to originate as an inflammation either of the mucous membrane of the smallest bronchioles, or of the connective tissue surrounding them (peribronchiolitis). It is supposed that the non-motile bacilli are carried through the superficial epithelium by the action of

leucocytes or of amœboid interstitial cells. The infection subsequently extends by the lymphatic channels. The pulmonary tissue between the tubercles is affected by catarrhal inflammation (bronchopneumonia), the intra-alveolar products thus formed undergoing subsequent caseation together with the interstitial inflammatory tissue.

The pleura may be affected in two ways: either as a result of an extension of the form of disease described above; or primarily, although this is rare in man. Tuberculosis of the pleura in its early stage is shewn, as a rule, by the growth of miliary granulomas beneath the pleura, and subsequently by the development of a large amount of fibrous tissue; in some cases, however, the tuberculosis leads to pus-formation and the production of an empyema. Some cases of empyema that occur in chronic pulmonary tuberculosis are probably not directly tuberculous, although this is not quite clear; but in the majority of cases the pus-formation must be ascribed directly to the presence of the tuberculous lesions in the lung. Extension of a tuberculous cavity by ulceration into the pleural sac, at a point where no previous adhesion of the two layers of pleura has occurred, may give rise to pneumothorax or pyopneumothorax.

Besides non-tuberculous empyema, there are other associated lesions in chronic pulmonary tuberculosis. Pneumonia may occur, as in a healthy lung; and in patients dying of chronic pulmonary tuberculosis bronchopneumonia and collapse are frequently found situated between the tuberculous lesions. The occurrence of bronchopneumonia in the course of advancing tuberculosis, or just before death, may sometimes be due to the inhalation of irritant bodies in the sputum, quite apart from tuberculous infection.

Dry pleurisy, occurring in the course of tuberculosis, is usually tuberculous, and is associated with the presence of tubercles on the pleura; effusion may result, the liquid of which may not contain tubercle bacilli; but even in this case the pleurisy is usually tuberculous. The opinion is gaining ground that the majority of all cases of pleurisy, both "dry" and exudative, which are apparently primary, no disease of the lung being at the time discoverable, are tuberculous in nature.

Tuberculous cavities may become secondarily infected by pyogenetic cocci, and occasionally by various moulds (*aspergillus, mucor*). Gangrene of the lung sometimes occurs, associated with thrombosis of the vessels and infection of the dying tissue by micro-organisms which are inhaled through the bronchial tubes.

(*c*) *Caseous Pneumonia.*—The great majority of the cases described under the heading Caseous Pneumonia are tuberculous. They present a very different appearance from that which has been described as occurring in chronic tuberculosis. There is more or less uniform consolidation over a greater or less area of the lung, and in what appears to be the less advanced stage of the disease the surface is granular on section, presenting a whitish-yellow appearance. In other parts there is caseation. Rarely a similar condition may be brought about by other micro-

organisms (pseudo-tuberculosis, pp. 290, 317), diagnosis being only rendered certain by the discovery either of the tubercle bacillus or of other fungi alone in the diseased tissue. Tuberculous pneumonia occurs as a sequel to a primary focus either in the apex of the lung or elsewhere.

(*d*) *Fibroid Tuberculosis.*—Fibroid tuberculosis occurs in three forms—as a localised nodule at the apex of the lung, as fibrosis of an area of lung affected by miliary tuberculosis, or as a slowly spreading fibrosis, associated with very chronic tuberculosis, lasting many years. Fibrosis is a feature in all cases of chronic tuberculosis of the lungs, and is the mode by which the tuberculous focus is encapsuled and infection of neighbouring or other parts prevented. The fibroid patches that are not uncommonly found at the apex of the lung are a form of what is called retrograde or obsolescent tubercle. Nodules varying in size from half an inch to an inch in diameter are seen, which on section shew a periphery formed of dense fibroid and pigmented tissue, frequently puckering the surface of the lung; and a centre, which is usually calcareous and may contain caseated matter. Where there is caseated matter tubercle bacilli are to be found as a rule, although they are scanty and stain badly with fuchsin, shewing that they are degenerated. Such fibrous nodules are but rarely infective. In three cases in which they were removed from the lung antiseptically, and introduced subcutaneously into guinea-pigs, no tuberculosis resulted (S. Martin). Fibrosis of a portion of the lung, usually the upper part, which has been affected with miliary tuberculosis without caseation, is not a common event; but it is sometimes observed in post-mortem examinations, when, as a rule, recent tuberculous lesions are found elsewhere. The part of the lung affected presents a dark appearance, is somewhat contracted, and is very tough; microscopically the alveolar structure is almost completely destroyed by the interstitial fibrosis, and the places where miliary granulomas existed are recognised by the indistinct appearance of nodules completely transformed into pigmented fibrous tissue.

The form of disease to which the term fibroid tuberculosis is applied clinically is that in which, as a result of a very slowly progressing disease, extending perhaps over many years and usually limited to one lung, there is extensive formation of fibrous tissue round the tuberculous lesion or cavity, from which fibrosis spreads into the rest of the lung. Associated with it, and as a result of the contraction of the fibrous tissue, there is extensive bronchiectasis. At the time when the lung is examined after death there may be little or no evidence that it is tuberculous, inasmuch as all caseous material may have disappeared, and the lung be one series of cavities, some of which are tuberculous, but most of which are bronchiectatic; these are surrounded by dense strands of connective tissue in which no trace of tubercle is discoverable. There is no other primary chronic disease that produces this condition of lung except tuberculosis, the fibrosis and bronchiectasis resulting from pneumonia being localised, and not as a rule extending beyond the original limits of the acute disease; while that associated with the inhalation of foreign particles

(pneumoconiosis) is bilateral in distribution. Besides bronchiectasis, the contraction of the scar-tissue found in fibroid tuberculosis may give rise to displacement of the heart, to contraction of one side of the thorax, and to resulting curvature of the spine.

Tuberculosis of the *larynx* is almost invariably secondary to disease of the lungs, the infection being conveyed by the sputum in its passage over the inter-arytænoid space. This region and the vocal cords are the structures most frequently attacked, but the epiglottis, the arytæno-epiglottidean folds, and the ventricular bands are also liable to suffer. The tuberculous process in the submucous tissue causes considerable swelling of the affected structures; ulceration generally ensues, the ulcers having somewhat ragged edges and granular floors on which caseous particles may be visible. In the rare instances in which the larynx is affected primarily the infection must either be conveyed by the blood-stream or result from direct inhalation of bacilli.

The peritoneum is affected in two forms: either as part of a general disease, or as a result of intestinal infection. When tuberculous peritonitis is part of a generalised tuberculosis the appearances are those of numerous miliary granulomas scattered over both the visceral and parietal peritoneum. They vary in number, and, if of long standing, are surrounded by a zone of pigment. Chronic tuberculous peritonitis is a result of intestinal tuberculous infection, but there may or may not be a local lesion in the intestinal mucous membrane. In well-marked tuberculous ulceration of the intestines there is very frequently a deposit of miliary granulomas in the peritoneum over the ulcers, which is congested at the spot or covered with a little lymph. But in children especially, intestinal tuberculous infection may lead to a generalised peritonitis. This is associated with enlargement and caseation of the mesenteric glands ("tabes mesenterica"), shewing that the course of infection was from the intestines. The peritoneum itself is no doubt in the early stages covered with miliary granulomas, although this stage of the disease is not often seen post mortem. When the disease becomes developed, the miliary granulomas have greatly increased in number, and have united, especially in the great omentum; and the great fibrosis, resulting from the presence of the tubercles, produces bands of thickened peritoneum stretching across the abdomen, binding the intestines together and frequently distorting them. As in the pleura when it is infected by tuberculosis, effusion may occur, which may be either a nearly clear straw-coloured liquid or pus. The pus may be bound down by adhesions and form a localised abscess. Such abscesses may extend through the abdominal wall or into the intestine; if perforation takes place in both directions, a fæcal fistula will result.

Meninges.—The pia mater is affected with acute miliary tuberculosis, either as part of a generalised tuberculosis, or by infection from an active focus elsewhere—for example, the joints, lungs, or intestines. The granulomas which occur are very small; they are seen in the interpeduncular space, and are situated along the vessels running into the Sylvian fissures.

They are present also in the lymphatic sheaths of the vessels which enter the brain from the pia mater, and they may extend backwards from the interpeduncular space into the part of the membrane lying in the transverse fissure of the brain. Pus is not infrequently present in the interpeduncular space, and is in most cases limited to the base of the brain. The formation of pus is due to the action of the tubercle bacillus itself; there is usually no secondary infection by pyogenetic cocci in tuberculous meningitis.

In the brain tuberculosis takes the form of nodules varying in size from a line to an inch in diameter, almost completely caseated, and usually surrounded by a capsule of unpigmented fibrous tissue. The nodules are quite discrete, and the caseated matter on section presents a peculiar greenish-yellow appearance. It is quite firm, and tubercle bacilli are usually to be found. The tuberculous nodule is always situated in the substance of the brain, and may be present in the hemispheres, commissures, cerebellum, pons, or medulla. In rare cases similar nodules may be found in the spinal cord.

Alimentary Tract.—Tuberculous lesions in the intestines may be primary or secondary, and may occur in the small or large gut. Tuberculous ulceration of the pharynx and fauces is extremely rare, and occurs only in cases where the lungs are affected. Tuberculosis of the œsophagus is a pathological curiosity; recently a case was described in this country by Drs. Shrubsall and Mullings. Rarely a small tuberculous ulcer may be found in the stomach, but only in advanced cases of tuberculosis, and when the secretion of hydrochloric acid is deficient. In the first part of the duodenum also, the contents of which are acid, tuberculous ulceration is extremely rare; but from the duodenum to the ileo-cæcal valve it is increasingly frequent, the chief parts of the mucous membrane in which it occurs being those in which the Peyer's patches are most numerous. Ulceration of the large gut may occur independently of that in the small gut, or both may be associated; but the large gut is not so frequently affected alone as the small. As elsewhere, the first sign of tuberculosis in the mucous membrane is seen in the deposit of nodules which coalesce and caseate, finally leading to necrosis of the superficial tissue and leaving an ulcer. The nodules may be present either in the deeper part of the mucous membrane or quite near the surface of a Peyer's patch. Both deep and superficial ulcers are thus formed. A fully formed tuberculous ulcer of the small intestine is not uncommonly transverse to the direction of the gut, but is chiefly characterised by its irregularity, by its thickened edges which are not undermined, and by its base, which is uneven, and shews a deposit of small caseated nodules, which may be situated either in the muscular tissue or in the peritoneum. Perforation of the ulcer into the general peritoneal cavity may occur, but as a rule this is prevented by adhesions to the neighbouring part of the gut due to the slight peritonitis produced by the ulcer. The result may be to mat the intestines together and to form irregular communications. Perforation in this form occurs almost equally in the small gut and in the

large. Stricture of the intestine may result from contraction of the scar of a healed tuberculous ulcer. A rare and remarkable condition characterised by great thickening of the walls of the bowel and narrowing of the lumen is known as chronic hyperplastic tuberculosis; it chiefly occurs in the neighbourhood of the cæcum (Lartigau). Infection of the tissue around the rectum gives rise to a common variety of fistula in ano.

Lymphatic Glands.—The early tuberculous deposits in the lymphatic glands occur as miliary granulomas, which rapidly caseate, unite together, and form the characteristic cheesy masses so frequently seen. This process commonly ends in calcification or fibrosis. In tuberculosis of the glands near the trachea or bronchial tubes, and of the superficial glands of the neck, axilla or groin, necrosis of the tissue superficial to the gland may occur, and the caseous contents of the gland be extruded, leaving a tuberculous sinus.

Bones.—Tuberculosis in the cancellous parts of the bones begins in a manner similar to that already described in other parts, soon leads to the formation of large caseous masses with disintegration of the bony tissue, and not infrequently to the formation of pus. This occurs in the "cold" abscesses that result, for example, from caries of the spine. Here, as in the meninges, the formation of pus is due to the action of the tubercle bacillus itself. The contents of the abscess are thick and ropy, and include numerous pus-cells in various stages of degeneration, besides yellowish masses of caseous matter. Tubercle bacilli are with difficulty found in the pus from these abscesses, and sometimes inoculation into animals fails to give a positive result.

Joints.—The deposit of tubercle in the joints occurs in the synovial membrane; it leads to great thickening, due to the formation of gelatinous fibroid tissue, and either to effusion into the joints or to the formation of an abscess. The bones forming the joints are also not infrequently affected by tuberculosis.

The kidneys are affected in two ways: either in the form of miliary granulomas, irregularly deposited through the substance of the organ, and most numerous in the cortex; or in the form of caseous masses, which are primarily formed in the apex of the pyramids and extend towards the cortex. In this way the whole substance of the kidney may be destroyed. In earlier stages miliary granulomas beginning to caseate are visible round the periphery of the caseous mass; that is to say, the primary focus has led to the formation of numerous secondary foci of tuberculosis. Extension of infection to the ureter and bladder may ensue.

The *epididymis, spermatic cord*, and *vesiculæ seminales* are not infrequently affected by tuberculosis; in all these cases the infection is conveyed by the blood-stream. The *Fallopian* tubes may also be the seat of tuberculosis.

Suprarenals.—Tuberculosis of these bodies, which is observed in Addison's disease, is usually seen (post mortem) as a complete caseation of the organ associated with fibrosis and calcification. Tubercle bacilli are with difficulty found in these cases. Whether the form of Addison's

disease associated with fibrosis and atrophy of the capsule be due to a primary tuberculosis of the organ or not, it is impossible to say. As a rule, in these cases no caseation or calcification is observed.

The liver and spleen are affected in a similar manner, viz. in the form of miliary granulomas. Tuberculosis of these organs is observed only as secondary to a tuberculous focus elsewhere. The granulomas, especially in the liver, are frequently microscopic only; but they may be a line in diameter, shewing a caseated centre. They project from the surface of the organ, and are also present in its substance. In the liver the nodules are very rarely large unless there be some secondary pyogenetic infection, as occurs sometimes in tuberculous empyema of the right side. Large tuberculous nodules are found in cattle and in pigs, but they are very rarely found in the liver of man ("solitary tubercle"). Infection of the bile-passages (tuberculous cholangitis) may give rise to multiple tuberculous "abscesses" throughout the organ. In the spleen caseation of the nodules serves to distinguish them from Hodgkin's disease. Caseous masses in the liver and spleen are less rare in children than in adults.

In the skin tuberculosis is seen in a very chronic form, as lupus. It is characterised by the same microscopical appearances as those which have been described, and the tendency is to necrosis of the cells and of the superficial tissues, leading to ulceration. Fibrosis is quite subsidiary in the extending disease, although it is well marked in the scarring which results from the healed ulcers. Many cases of so-called "anatomical tubercle" (*verruca necrogenica*) are due to the *Bacillus tuberculosis*, as are also some other forms of chronic inflammation of the skin (*tuberculides*).

Pathology.—The anatomical characteristics of tuberculosis, both from the histological point of view and from the manner in which the disease affects individual organs or parts, are but a very small part of the subject of tuberculosis as an infection. Not only must the proof that the *Bacillus tuberculosis* is a necessary factor in the disease be discussed, but the question of the modes of infection, and of the parts affected by these different modes, as well as the spread of the disease in the body from a local focus, must be considered. In connexion with this, too, arises the question of the usual source of infection in man, as well as the questions of the effect of dose and virulence of the virus, and of the resistance of the body to its invasion and spread.

The Bacillus Tuberculosis as a Cause of Tuberculosis.—This bacillus has been definitely proved by the experimental method to be a necessary factor in the causation of tuberculosis in the following manner:—

(*a*) The bacillus is found in tuberculous lesions both in man and animals. In a particular lesion the bacillus may be absent, having died; but in one or other lesion of the body of a tuberculous animal, and in nearly all recent tuberculous lesions, tubercle bacilli are readily found.

(*b*) The bacillus has been separated from tuberculous lesions in man and cows, and from the sputum in man, and obtained in pure cultivation.

(*c*) Inoculation into susceptible animals of the tubercle bacillus,

obtained in pure cultivation, produces exactly the same disease, both anatomically and in the mode of distribution of the lesions, as in man or animals which suffer naturally from tuberculosis.

(*d*) From the lesions in the experimental cases in animals the bacillus can be obtained in pure cultivation, living and virulent.

These facts do not rest on any single series of experiments, for since their discovery in 1881-82 by Koch, they have been repeated and confirmed by numerous observers, and receive, indeed, continual confirmation in every pathological laboratory. They serve, then, as the basis of discussion of the pathology of tuberculosis.

Modes of Infection.—In investigating the modes of entrance of the *Bacillus tuberculosis* into the body, it is important to remember that the infection may, on the one hand, remain localised at the point of entry, or may, on the other hand, be carried to distant parts, leaving little or no trace of the path by which it has travelled. As examples of local tuberculosis occurring at the seat of invasion, primary pulmonary tuberculosis may be quoted, or intestinal and peritoneal tuberculosis, or tuberculous lymphatic glands in the neck. On the other hand, the disease may be localised in parts far removed from any of the paths by which the virus enters the body—as, for example, when tuberculous joint-disease occurs in an individual who apparently has no other tuberculous lesion.

The great number of questions which arise in the consideration of these points are for the most part answered by the results of experimental tuberculosis in animals. Such experiments afford material of the highest importance in the study of the disease; inasmuch as the effects of dosage, virulence of the bacilli, and resistance of the body to the infection can be gauged. The effect of the resistance of the body is readily determined by observing the effects of the same dose of virus in susceptible and refractory animals—in guinea-pigs and rabbits, for example, which are susceptible animals, and in dogs and some species of rats, which are refractory animals.

Experimental Tuberculosis.—The following points will be considered in discussing experimental tuberculosis :—

(*a*) Variations in the intensity or rapidity of the disease after inoculation or feeding or inhalation of tuberculous material.

(*b*) The virulence of different forms of tuberculous material.

(*c*) The varying effects of dose on the extent of the tuberculosis produced.

(*d*) The formation of a local lesion or not at the seat of entrance of the virus into the body.

The resistance of the body to the invasion of the disease—that is, natural immunity—will not be considered in the following discussion, which relates only to animals susceptible to the disease—namely, guinea-pigs, rabbits, calves, and pigs. Calves and pigs are both subjects of natural tuberculosis; but in guinea-pigs and rabbits tuberculosis is unknown outside the laboratory. These two animals, indeed, especially

the guinea-pig, kept under hygienic conditions, serve as excellent and accurate tests of the infectivity of any particular tuberculous material.

Inoculation Experiments.—In guinea-pigs inoculated subcutaneously in one or other groin by virulent tuberculous material, as early as nine days after inoculation a local lesion is seen which, on microscopical examination, may be recognised as tuberculosis. The inguinal glands become tuberculous in from seven to fourteen days, and about the third week after inoculation the disease spreads to the internal lymphatic glands, always invading the lumbar glands, and usually affecting the cœliac glands before it spreads to the liver and spleen. Spreading to the thorax (which it does about the fourth week), it affects first the posterior mediastinal and bronchial glands; and subsequently, about the fifth week, the lungs. The mesenteric glands are affected only in very advanced tuberculosis following inoculation. The suprarenals and the kidneys are never found affected by the disease.

If the tuberculous material be inoculated in both groins the disease is developed on both sides—that is, both inguinal and both lumbar groups of lymphatic glands become affected; whereas if one side only be inoculated the lumbar and inguinal glands of the other side do not become tuberculous, although the lumbar glands may become so in the later stages of advanced tuberculosis in the guinea-pig.

The intraperitoneal inoculation of virulent tuberculous material produces an intense tuberculous peritonitis, with great thickening of the omentum and the deposit of miliary tubercles over both the parietal and visceral peritoneum: this is evident in from ten to fourteen days after inoculation. In fourteen days tuberculosis of the lumbar, cœliac, anterior and posterior mediastinal lymphatic glands may be evident, and, if very virulent material be used, tuberculosis of the liver and spleen or even of the lung. In sixteen to twenty-one days practically every organ of the body may be affected, except the gastro-intestinal tract, and, in the guinea-pig, the suprarenals and kidneys. The mesenteric glands become affected at a very late stage of the tuberculosis, and ulcers of the intestines are never produced by the inoculation of tuberculous material wherever introduced. Inoculation into the anterior chamber of the eye produces, in seven to ten days, a local tuberculosis, which then spreads to the neighbouring lymphatic glands, and finally to the lungs and other organs of the body.

The inoculation of sputum from cases of human pulmonary tuberculosis as well as of material obtained from recent and progressing lesions of the disease, produces similar effects, viz.: (1) a local lesion; (2) a spread of the disease to the lymphatic glands nearest the local lesion; (3) the invasion of the solid organs of the body. Sputum, no doubt, has a varying infectivity, dependent on the character of the lesion which produces it, whether, that is, it contains a large number of living tubercle bacilli or not. Not many experiments, however, have been performed from this point of view. Of great importance in human pathology is the result of inoculating the meat and milk from tuber-

culous animals into guinea-pigs and rabbits, since we are thus enabled to study the results of inoculation with material of comparatively low virulence. The milk from a cow with tuberculosis of the udder may be highly infective, or only slightly so; and the infectivity is due to the presence of tubercle bacilli in the milk, coming, as in the sputum of pulmonary tuberculosis, from the breaking down of tuberculous lesions. The meat from tuberculous cattle may also be highly or only slightly infective; but in this case the infectivity does not depend on the presence of tuberculous lesions in the muscular tissue itself, but on the contamination of the meat, during its removal, by or from the tuberculous lesions present in the carcase.

The effects resulting from the inoculation of meat and milk into animals vary with the dose of the virus present in the inoculated material; inasmuch as, apart from the dose, the virulence of the bacilli in a particular lesion cannot at present be gauged. In a highly infective disorder, such as anthrax, where death follows inoculation in twenty-four or thirty-six hours, the dosage is not of so much importance as the virulence or vitality of the bacillus. That is, speaking broadly, twice the fatal dose of material containing anthrax bacilli will not produce a greater effect in a guinea-pig than a smaller dose. But in the case of anthrax bacilli the virulence may vary greatly, and produce corresponding effects in the animal body. With tuberculosis, however, dosage is of greater importance, inasmuch as the larger the dose, within limits, the greater the degree of tuberculosis produced in a susceptible animal. For tuberculosis is essentially a chronic disease, one in which the infective agent grows slowly; therefore with a small number of bacilli the body is more likely to resist their invasion and to restrict their action to the seat of inoculation, whereas with a large dose this defensive action is not so effective. The importance of "dosage" is illustrated by Dr. S. Martin's experiments[1] with tuberculous milk. One cubic centimetre of virulent milk injected into the peritoneal cavity produced in sixteen days, besides the local lesion of the peritoneum, tuberculosis of all the internal lymphatic glands, of the cervical glands, and of the liver and spleen, but not of the lungs; whereas one cubic centimetre of a 10 per cent dilution of the same milk produced in the same time a local lesion practically limited to the omentum, with tuberculosis of the spleen and of the mesenteric glands, but of no other parts. Dilution of the milk thus produced in the same time a limitation of the disease. Inoculation with the meat of tuberculous animals even more clearly emphasised the same principle, a guinea-pig inoculated with material of this nature exhibiting merely a localised tuberculosis of the skin at the point of infection, with no sign of general invasion of organs.

Baumgarten found that injection of cultures of tubercle bacilli into the bladder produced in animals a tuberculosis of the lungs, and a similar result was obtained by Behring from injections into the substance of the

[1] Details of these and other experiments were given in the first edition of this *System*, Vol. II. p. 19 et seq.

tongue. These observations have been used to support the opinion that ordinary pulmonary tuberculosis is hæmatogenous in origin, and is not produced by direct inhalation of infective material.

Feeding Experiments.—Inoculation-experiments, although instructive from the point of view of infection, do not reproduce the kind of cases that occur in the human being or in natural tuberculosis. Although inoculation-tuberculosis has occurred in the human being, the great majority of cases of the disease are to be ascribed to other modes of infection. Feeding is one of these.

If guinea-pigs be fed with one dose of virulent tuberculous material obtained from the cow or man, the first lesion observed, as in other cases of infection by the disease, is a local one in the small intestine and cæcum. This is first apparent to the naked eye (and, indeed, to microscopical examination) at the end of from eighteen to twenty-one days. The frequency with which the small intestine or the cæcum is affected is variable. Of twenty animals rendered tuberculous by feeding, the disease was present in the small intestine in all but one, which had been fed with sputum; and the cæcum was affected in all but three. The frequency of the infection of the cæcum in the guinea-pig is explicable by the presence of large and numerous Peyer's patches, a point of difference from the condition in man and carnivora. From the intestines the disease spreads to the mesenteric and the cæcal lymphatic glands in about twenty-eight days from the commencement of the experiment; from these it spreads to the cœliac glands, the liver, spleen, posterior mediastinal and bronchial glands, and to the lungs. In some animals, living a long time, the anterior mediastinal glands are affected; as are also the glands in the lesser omentum and the lumbar glands.

In pigs fed with virulent tuberculous material the pathological course of the disease is practically the same as in guinea-pigs; namely, from a local lesion in the alimentary tract the infection spreads to the neighbouring lymphatic glands, and thence to the organs of the body. But in the pig the tonsil is one of the chief localities for the absorption of the tuberculous virus. In one of Dr. Martin's experiments a pig which had received at one meal 120 grammes of tuberculous lung exhibited, when killed, as the sole lesion in the whole alimentary tract, a small ulcer, $\frac{3}{4}''$ by $\frac{1}{2}''$; but in addition there was extensive tuberculosis of lymphatic glands and of the other viscera. This experiment is of importance, as shewing that the local lesion from feeding may be out of all proportion to the tuberculosis present in the organs of the body.

In calves fed with virulent tuberculous material the local lesion is present in the small intestine, and less commonly in the cæcum. The mesenteric glands are always affected, and, when the cæcum is attacked, the cæcal glands. The disease then spreads to the posterior mediastinal and bronchial glands, and usually to the lungs. The cervical glands may be subsequently affected, as well as the retro-hepatic glands. Two points, however, must be noted: (1) That, as in the pig, the glands below the jaw may be affected, shewing that the absorption of the virus has

taken place through the pharynx; and (2) that tuberculosis of the pleura in the form of "grapes" may occur without any infection of the lungs. This result is of some importance from the pathological point of view.

In both pigs and guinea-pigs feeding with non-virulent tuberculous material may result in a generalised infection, without the existence of any discoverable local lesion at the point of entry of the bacilli. The path of infection may, however, generally be traced by observing the lymphatic chain mainly involved. In pigs extension of infection from the tonsil to the cervical glands, and thence to the lung, may occur, the process closely resembling that which takes place in human subjects.

In the experiments on calves fed with either virulent or slightly virulent tuberculous material there was always a local lesion in the intestine when tuberculosis developed; but it is noteworthy that the local lesions in the intestines frequently did not proceed to ulceration, but consisted in small nodules in the Peyer's patches, which caseated, and frequently became calcareous. Calcification of these nodules was sometimes found, even though there was active and spreading tuberculosis in various organs of the body. A similar observation was made in adult cows, the subjects of natural tuberculosis; and the same thing occurs in the human being—the main point is that the local lesion is out of all proportion to the tuberculosis which subsequently develops throughout the body. To calves human sputum is not so highly infective a material as the tuberculous material from the organs of a cow. Different breeds of cattle vary in their susceptibility to infection, a pure Jersey cow, for example, being less resistant than a half-bred shorthorn.

Inhalation Experiments.—Numerous inhalation experiments have been performed (Villemin, Koch, and others), with the result of transmitting the disease to animals. The bacilli in pure cultivation have been sprayed on to the faces of animals, and a pulmonary tuberculosis has resulted; and tuberculous material has been dried and powdered, and allowed to be inhaled by the animals, with the almost certain result of producing pulmonary tuberculosis. This experiment, however, is dangerous for the workers, one of whom contracted a fatal tuberculous bronchopneumonia in this manner (Nocard).

Modes of Infection in Natural Tuberculosis in Animals.—In cows the mode of infection is either by means of the lungs or the intestines. In cases of tuberculosis in cattle the lungs and pleura are affected in about 40 per cent of the cases; the lungs alone, in 20 to 25 per cent; the pleura and peritoneum, in 15 to 20 per cent, and in the remaining cases the lymphatic glands, the genital organs, mammæ, bones, etc. (Nocard). This, however, is not a valuable mode of classification, except to shew that, as in man, tuberculosis in the majority of cases affects the lungs and thoracic organs. The analysis of twelve cases of natural tuberculosis in the cow, in which every organ and gland of the body was examined, gave the following result:—The disease was primary in the lung in eight cases; primary in the intestines without affection of the lungs in one case; and in the intestine with affection of the lungs in three cases.

The statement that these last three cases were primary in the intestine rests on the conclusion that the intestinal lesion, being calcified, was older than that in the lung. In cattle, therefore, the disease must be considered as most frequently an inhalation-tuberculosis, and less frequently an ingestion-tuberculosis. In the cow, when the lungs are affected, the posterior mediastinal glands are usually tuberculous; and, except in certain cases which occur in children, this constitutes an anatomical difference between pulmonary tuberculosis in the cow and in man. The disease, as it occurs in the cow, may thus be divided into two classes, namely, (1) where it is limited to the thoracic organs and glands, and (2) to the abdominal organs and glands. In cases of disease in the thorax it is highly probable, even if only one set of glands in the abdomen be affected, especially if this be the mesenteric glands, that the mode of invasion of the virus has been through the intestines. Thus, cases occur in which there is extensive tuberculosis of the lungs, of the bronchial and posterior mediastinal glands, of the glands in the lesser omentum, and of the liver. In such cases it is probable that the glands of the lesser omentum are first affected, the disease spreading thence to the liver, to the posterior mediastinal and bronchial glands, and thence again to the lungs.

In the pig the disease is almost solely an ingestion-tuberculosis, produced by feeding with the flesh or milk of tuberculous cattle, and has the features which have been described previously.

In the horse, infection occurs both through the intestines and through the lungs, most frequently, however, by the former mode; so that in most cases the abdominal organs are the chief ones affected, well-marked peritonitis being observed. This does not occur in the cow or the pig. The lung is usually affected secondarily.

Modes of Infection in Man.—In human tuberculosis, many as are the years during which it has been the subject of study, there is a great want of accurate information as regards the distribution of tuberculous lesions in a large number of cases; yet it is only by a consideration of large numbers that the modes of infection can be determined. The three modes of infection by which tuberculosis can occur after birth are by the inoculation, by feeding, and by inhalation of tuberculous material. Infection may be carried from the mother to the fœtus in utero.

Inoculation-tuberculosis occurs accidentally in the human being, as in cases of wound of the hand during a post-mortem examination of a tuberculous subject. Some of the warts which appear in these cases (*verruca necrogenica*) are of a tuberculous nature. Death from pulmonary tuberculosis has also been known to follow inoculation of the finger after a longer or shorter interval. Possibly lupus is in some cases a form of inoculation-tuberculosis, following infection of the skin with non-virulent tuberculous material, as in the case of local tuberculosis of the skin in a guinea-pig (*vide* p. 275).

The more usual modes of infection in man, however, are by way of ingestion and of inhalation. Speaking generally, ingestion-tuberculosis

is a disease of childhood, inhalation-tuberculosis a disease of young adult life, although it may occur at all ages. When the lungs alone are the seat of tuberculosis at death, as they so frequently are, and no old or recent tuberculous lesion is found in or near any part of the alimentary tract, the mode of infection almost unquestionably was by inhalation of tubercle bacilli. Similarly with the intestine: in cases where there is tuberculous ulceration of the intestine, or even tuberculous nodules in the intestine, with tuberculosis of the mesenteric glands or peritonitis, and no infiltration of the lungs, the mode of invasion has doubtless been by way of the mucous membrane of the intestine. But there are many cases which present great difficulties in their explanation—cases of so-called primary tuberculosis of the bones and joints, of the kidneys, of the epididymis, and of the brain or meninges. Post-mortem records of these have not been made with sufficient accuracy from the present point of view to permit us definitely to indicate the mode of infection in many of them. In some cases of primary tuberculosis in the parts mentioned old lesions are found, either in the lungs or intestines; for example, in cases of meningitis a few healed ulcers may be found, or a calcareous mesenteric gland; and in cases of tuberculosis of the epididymis, where fibroid and calcareous nodules are found in the lungs there is no difficulty of explanation. But there are cases in which no local lesion, old or recent, can be found in the lungs, the intestines, or the neighbouring lymphatic glands. The explanation of such cases appears to be given by the results of the previously recorded experiments in animals (p. 277), which have shewn that the tubercle bacilli may enter the body without producing a lesion in the mucous membrane; and that even if one of the glands in connexion with the gastro-intestinal tract become tuberculous, this may readily lead to disease of a distant part. It is quite possible in the tissues of children, in which absorption is active, that tubercle bacilli may pass even through lymphatic glands without producing a lesion; or more probably may enter the circulation from the mucous membrane and be carried to a distant part—such as the joints, bones, or the meninges—and so produce primary tuberculosis in those parts. In any case, whatever the exact path of infection, it is certain that the bacillus must pass through some portion either of the gastro-intestinal or of the respiratory tract.

Spread of the Disease in the Body after Infection.—Two classes of cases have to be considered, in one of which (and these are the majority) a local lesion is produced at the seat of infection; in the other there is no local lesion, but either a lymphatic gland in connexion with the organs which usually constitute the path of the infection is affected, or, without infection of the lymphatic glands, a distant part may be affected by the tuberculosis primarily. When there is a local lesion in the early stages of the disease, a spread of infection takes place mainly by lymphatic channels, as has been fully explained in the account of experimental tuberculosis; but infection also occurs by actual contact of the tuberculous lesion with neighbouring parts, this being most evident in the lungs, and in cases in which the pleura

infects the peritoneum after adhesion to the diaphragm. With these may be classed the instances in which bacilli conveyed in the urine from a tuberculous kidney infect portions of the lower urinary tract, and those in which tuberculous sputum causes secondary tuberculosis of the larynx or the intestine. The third mode of spread of the disease is by means of the blood-vessels; this takes place when the blood-vessels are themselves involved in the tuberculous process, as in the lungs they very commonly are; the tuberculous lesion ruptures into the lumen of the vessel, and the virus is carried to distant parts. An actual tuberculosis of the intima of vessels also occurs. In this way the occurrence of tuberculosis of the liver and spleen in primary tuberculosis of the lungs is explained, the occurrence of meningitis likewise, and the infection of such distant parts as the joints and bones. Instances of tuberculosis have been described in the fœtus when born, or in the early months of life, and are attributable to infection directly derived from the mother. It is evident that this can only occur when there is tuberculosis of the placenta, for there is no actual continuity between the blood-vessels of the mother and those of the fœtus, and the tubercle bacilli cannot be supposed to find their way through the walls of uninjured vessels.

Cases of primary tuberculosis in the bones, joints or epididymis—that is, in parts far removed from the ordinary channels of infection—may lead to a generalised tuberculosis: inasmuch as there is no direct lymphatic connexion between the parts affected, the spread of the disease in these cases takes place presumably by means of the blood-vessels.

Sources of Infection.—Tuberculosis has all the characters of an infective disease. It has an incubation-period; it is associated with fever, and with certain other definite symptoms which will be discussed later. The long duration of cases of tuberculosis was formerly the great bar to the acceptance of the disease as an infective malady, but at the present day the infectious character of the disease is well recognised, and there is even danger of an unnecessary panic, tending to cause tuberculous patients to be shunned as pariahs, due to lack of appreciation of the nature of the infection. This is very different from that of such diseases as scarlet fever or typhus, precautionary measures of a simple kind sufficing to abolish the risk of infection arising from tuberculous patients.

Tuberculosis is an infection; it is due, that is, to a virus which is introduced into the body; it cannot arise *de novo* in the body. Consequently the sources of infection are deserving of the closest study, since it is by such knowledge alone that we are enabled to devise the measures necessary for the prevention of the disease. The bacillus is a parasite, not a saprophyte, and has no independent existence outside the body. But there are numerous sources of infection by tuberculous material from human beings or from animals the subjects of the disease. Thus, from human beings there is the sputum from the lungs in pulmonary tuberculosis; the urine or the fæces, when the urinary tract or intestines are affected with the disease; and the discharges from tuberculous ulcers and fistulæ. Milk from a tuberculous cow may be a source

of infection, or meat from cow, pig, or fowl; and tuberculous organs or parts removed from man or animals may also be sources of danger. By far the most important of all these, however, are sputum and milk.

1. *Sputum* in the moist state, when inoculated, inhaled, or used for feeding, produces a spreading tuberculosis, as has been frequently proved by experiment. In dried sputum the bacilli retain their vitality for a very long period, even for eight or twelve weeks; and in this form they can produce tuberculosis in animals by inhalation. Considering the number of tuberculous human beings in the world, and the absence of precaution in the treatment of the sputum, this is probably the most frequent cause of tuberculosis, and especially of tuberculosis of the lungs. The dangers from sputum arise not so much in the open air, as in the habitation or the room occupied by a patient. In the open air it is soon dried, and the bacilli are rapidly killed by means of the sunlight. In the room occupied by the consumptive, not only does the handkerchief, which frequently receives the expectoration, become highly infective, but also the clothes of the patient, the bed-clothes, and the walls and furniture; soiled handkerchiefs may be laid on the mantelpiece or elsewhere; expectoration may fall upon the floor. Thus, the room in which a consumptive has lived, especially towards the end of the disease when he is in bed and occupies one only, becomes highly infective if no precautions be taken to disinfect or destroy the sputum; even when spitting-cups are used, these have been known to transmit tuberculosis by inoculation to the person who washes them, as by way of wounding a finger. Considering that sputum is a tenacious material, that it is readily collected in a vessel, and that its infectivity is readily destroyed, either by antiseptics (carbolic acid) or by heat, there can be no doubt that if proper precautions were taken in destroying this highly infective material much progress would be made on the road to prevention of the disease. Many instances of direct infection by sputum have been recorded, some of which have occurred after inoculation. Thus in addition to such occurrences as have already been mentioned, in which a finger was wounded in cleaning utensils containing sputum and was thus infected, cases are recorded in which tuberculosis of the prepuce and inguinal glands has followed circumcision performed according to the Jewish rite by a consumptive priest. Direct infection by sputum, causing pulmonary tuberculosis, was conveyed by a midwife, the subject of advanced pulmonary tuberculosis, who was accustomed to blow down the mouths of newly-born children: no fewer than ten of these became tuberculous. To this category also belong those cases in which a healthy husband contracts tuberculosis from a consumptive wife, or vice versa.

It must be borne in mind that not only is the actual expectoration of tuberculous patients infective, but particles of mucus expelled in the act of coughing also contain virulent bacilli; the "spray" of the cough is thus an important source of infection, especially in advanced cases of pulmonary tuberculosis.

2. *The milk* from cattle, the subjects of tuberculosis of the internal organs and of the udder, if consumed in the raw state, is another source of infection. When the udder is not diseased the milk is not infective, and never contains tubercle bacilli; although it must be remembered that tuberculosis of the udder may supervene at any time in a tuberculous cow. Experimentally this has been definitely proved. With the milk of eight cows, the subjects of tuberculosis in varying degrees from a very slight amount of disease to advanced and generalised tuberculosis, but without disease of the udder, twenty-six animals (rodents) were inoculated, and forty-one animals (guinea-pigs, pigs, and rabbits) were fed; none developed tuberculosis. On the other hand, when the udder is diseased the milk usually contains tubercle bacilli, which are discoverable on a microscopical examination. If the disease, however, be not far advanced, it may be difficult or impossible, within practical limits, to discover tubercle bacilli, although these, as shewn by the results of inoculation and feeding, are present. Thus, to quote the experimental results: with the milk of five tuberculous cows, suffering from tuberculosis of the internal organs, varying in degree, and with varying degrees of tuberculosis of the udder, twenty-one animals were inoculated—all developed tuberculosis; twenty-seven animals were fed—nineteen developed the disease. The milk given by such cows is, therefore, very virulent, and must be considered as the chief mode by which an ingestion-tuberculosis occurs in man. The butter made from such milk (even when diluted with normal milk), the buttermilk, and skim-milk are also highly infective, and produce tuberculosis both by inoculation and by feeding.

Milk is a source of infection chiefly in children, for whom in the early years of life it ought to form the chief article of diet; to the ingestion of milk are no doubt to be ascribed a large proportion of the cases of intestinal tuberculosis and of tuberculous peritonitis that occur in children. In some instances it has been directly shewn that milk is a source of infection in childhood (Demme), producing intestinal tuberculosis. Some cases where tuberculosis has affected the socket of a lost tooth are also possibly ascribable to milk. It must be granted, from the experiments in pigs, to which allusion has already been made, that it may likewise be a source of tuberculous (scrofulous) glands in the neck. The sputum, or any tuberculous material that gets into the mouth, may of course affect these glands also, and children crawling about on the floor are liable to get their hands infected; thus tubercle bacilli have been found under the nails of young children (Dieudonné). The practical importance of such a mode of infection is difficult to estimate. As far as milk is concerned the danger is no doubt diminished, because in large towns the milk of all the cows of a herd is mixed, producing a more uniform quality. But this is not always so; the milk of a single cow is, from an erroneous belief in its superiority, frequently used for feeding children; and even when such milk is mixed with non-tuberculous milk, it is quite possible for one individual to get a sufficient dose of the virus to produce tuberculosis. Infection by milk is prevented by boiling it for at least a

minute. As soon as tuberculous cattle are rigidly excluded from the dairy it can scarcely be doubted that there will be a great diminution in cases of abdominal tuberculosis in children. The proportion of primary abdominal affection in this country is calculated by Dr. Still and by Dr. Shennan as approximately 30 per cent. In the United States it is apparently much lower (under 2 per cent, Bovaird), and also on the continent of Europe, Biedert finding only sixteen cases of such primary disease in 3104 autopsies, and Baginsky failing to find among 933 cases a single instance in which the abdominal organs were alone affected.

3. *The meat* removed from tuberculous cattle is infective in a varying and somewhat irregular manner. Experiment has shewn that the infection depends, not on tuberculous lesions in the muscular tissue itself, but on the contamination of the meat during its removal from the carcase; either by the meat touching a tuberculous part, or by infection from the butcher's knife or cloth which has previously incised or wiped a tuberculous part. Besides this superficial contamination, tuberculous glands, either the lumbar or popliteal glands, are not infrequently left in the carcase when sold, and these might in some instances be imperfectly cooked, and, containing living bacilli, would when swallowed be a source of danger. Tuberculous lesions of the muscular tissue itself are extremely rare, and do not account for the tuberculosis which results from the inoculation or feeding of animals with the meat. The results of experiments made to test the infectivity of meat may be quoted. Meat from twenty-one cows, which were in varying stages of tuberculosis from mild to advanced, was inoculated into forty-eight animals; of these, ten developed tuberculosis: 102 animals (guinea-pigs and pigs) were fed on it, and six developed tuberculosis (S. Martin). It is thus seen that raw meat is a much less infective material than raw milk. The danger of meat in the production of tuberculosis is diminished by cooking, since by any mode of cooking—whether roasting, broiling, or boiling—the surface of the meat is raised to a temperature which is fatal to the tubercle bacilli contained in the tuberculous material contaminating it. Raw meat is sometimes given medicinally, and, unless precautions be taken, this may be a source of tuberculosis. The more advanced the tuberculosis of the cow, the more likely is the meat to be infective; therefore, no meat ought to be passed for use as food from a cow in which the anatomical distribution of the disease shews that it has become generalised.

Tuberculous pigs constitute a specially dangerous source of food, since in these animals the disease is apt to become generalised, and it is difficult to separate the infected from the sound parts of the carcase.

4. *Tuberculous organs or tuberculous parts* removed by operation, as well as the normal excreta from organs which are the seat of the disease, may be sources of infection in tuberculosis. Organs from the slaughter-house given to animals may produce tuberculosis in them, and all tuberculous parts when dried may, like the sputum, be sources of infection. All such parts ought either to be destroyed by heat, as in the case of solid organs and parts, or rendered sterile by antiseptics, as in the case of urine and

fæces; these precautions would prevent at least some of the cases of tuberculosis in animals, and possibly in man also.

Preventive Measures.—It is evident from what has been said of the sources of infection that they are all preventible. As regards the milk and the meat, public regulations for limiting the supply of milk to that from healthy cows alone, and for preventing the sale of meat from cattle in an advanced stage of tuberculosis, are necessary; and would, no doubt, in time remove meat and milk from the list of sources of tuberculous infection. Public regulations, however, develop slowly, and not infrequently are imperfectly carried out; but as regards milk, tuberculous infection is so readily destroyed by boiling that this ought to be done as a precautionary measure by every householder. Similarly with the meat from tuberculous cattle, to sterilise the surface would, in the majority of instances, be sufficient to destroy the infectivity of the material. The destruction of tuberculous organs removed in the slaughter-house ought to be compulsory, and such organs ought not to be used in any way whatever. No part of the carcase of a tuberculous pig should be used for food. Efficient inspection of all meat intended for sale must be carried out, and it has been suggested that fixed stations should be established for the examination of all meat brought, for instance, to London, the introduction of meat by other routes being prohibited. Stringent supervision of all slaughter-houses is absolutely essential, and the substitution of public abattoirs for private yards is urgently called for, as the only means of rendering such supervision possible.

The destruction of parts removed by an operation is usually effectively performed; when preserved in alcohol the tubercle bacilli are killed, and when not preserved the parts are usually burnt. The urine can only be a source of infection in tuberculosis in rare instances; but it is evident (inasmuch as intestinal tuberculosis with diarrhœa is so common an infection both in man and animals) that the fæces, after drying in the stall, or after contaminating the bed-pan, may frequently be a source of infection. In the case of human beings the use of antiseptics, such as carbolic acid or hydrochloric acid, is sufficient to destroy the infection; and cattle, when they come to the stage of an exhausting diarrhœa due to intestinal tuberculosis, ought to be slaughtered and the stalls disinfected. Lastly, the sputum is a preventible source of infection. No state regulations will make people careful in the disposal of tuberculous sputum; but as soon as consumptive individuals are educated to understand that the sputum which they bring up from the lungs is a source of danger not only to those surrounding them, but to themselves, and that the danger can be obviated by a very little care, precautionary measures will, no doubt, be taken by these persons, and in this way the most common cause of pulmonary tuberculosis will be prevented. Patients with pulmonary tuberculosis should be instructed to occupy, if possible, separate bedrooms; to cough only into a special handkerchief which can be daily disinfected or destroyed; to use a special receptacle for the expectoration, which must be carefully sterilised; and to avoid kissing the members

of their families on the lips. The necessary instructions and advice may be given either by special Health-visitors or by leaflets distributed at hospitals and dispensaries.

A serious danger undoubtedly arises from cases of advanced tuberculosis of the lungs occurring in poor persons who cannot receive due care and assistance. Hospitals for such cases should be provided by municipal authorities, just as they are now provided for the acute infective fevers. To facilitate measures of isolation and disinfection, as well as the dissemination among sufferers of knowledge as to the nature of the risks involved, and of the measures to be adopted to obviate them, compulsory notification of the disease to the Health Authority should be instituted, due care being taken to adapt the measures taken to the real needs of the case, avoiding any unnecessary disturbance of family relations and the creation in the mind of the public of any exaggerated fear of the contagiousness of tuberculosis. Rooms which have been occupied by patients dying of consumption should be carefully disinfected.

Tuberculosis is not a disease in which the infective agent, the tubercle bacillus, is so widely distributed that no precautionary measures are available against its spread and its invasion. The bacillus is not a saprophyte. It exists only in tuberculous lesions and in the products of their degeneration; thus, in the human being tuberculous infection tends to become limited to places inhabited by consumptives; and in cattle it is a disease of the stall.

Immunity is either natural or acquired. In tuberculosis, under certain conditions, there is a relative local immunity of some tissues and organs which prevents their invasion by the disease. There is a natural immunity both in some men and in some animals; thus certain races of mankind (*e.g.* Jews) suffer comparatively little from tuberculosis, and some species of animals, such as the Carnivora in a wild state, never exhibit spontaneous tuberculosis.

Local Immunity of Tissues.—This has already been indicated in discussing the parts most frequently affected by tuberculosis, but there are certain parts so rarely affected by the disease that they may be considered naturally immune. When tuberculosis affects man or animals it is a local disease, inasmuch as, however many parts may be affected, only those parts that contain the lesions are infective, and each focus of disease has, so to speak, a separate existence and course of its own. Parts of the human being which are relatively immune to tuberculosis are the mucous membranes of the mouth, pharynx, œsophagus, stomach, and first part of the duodenum. Not that tuberculosis has never been observed in these parts, but it occurs very rarely, and only in advanced cases of the disease. The absence of infection of the pharynx and œsophagus in tuberculosis is to be explained by the rapid passage of the infective material through them in swallowing, the mucous membrane being, moreover, protected by stratified epithelium. In the stomach and first part of the duodenum the hydrochloric acid in the gastric juice prevents the development of the tubercle bacillus, and may even be

fatal to it. Muscular tissue is rarely affected by tuberculosis, and this, again, is perhaps to be ascribed to the acid which is formed by the muscles during their contraction; in an acid medium the tubercle bacillus cannot grow. Tuberculosis of muscle, however, does occur, but only in advanced cases of the disease, and chiefly in animals. The thyroid gland is another part which is very rarely infected. Reference has already been made to the relative immunity of the kidneys in cases of experimental tuberculosis in guinea-pigs. In rabbits, on the other hand, the kidneys are frequently affected in generalised tuberculosis, and they are affected in cattle, pigs, and other animals, as well as in man.

Immunity to Natural Tuberculosis is only a relative term; it does not mean that the disease cannot be conveyed to animals by inoculation or feeding. Animals differ in the frequency with which they are naturally liable to the disease, and in their resistance against the inoculation of tuberculous material. Tuberculosis is a natural disease in man, cattle, pigs, and birds in a state of domesticity. It is rare in sheep, goats, horses, dogs, and cats. It is a disease, therefore, of man who lives in houses, and of cows which are kept in stalls. In spite of the high mortality caused by tuberculosis, mankind appears to be somewhat refractory to the infection. Thus, healed tuberculous lesions are commonly found at necropsies on persons who have died from other causes, shewing that spontaneous cure frequently takes place; indeed Naegeli states that the bodies of all persons over thirty years of age, if completely examined, shew traces of some tuberculous lesion. In view of this observation, and of the good effects produced in tuberculous subjects by such conditions as an open-air life and plentiful feeding, as well as of the influence of insanitary surroundings in producing the disease, it seems probable that in an ideal human community, the members of which were adequately fed and clothed and lived healthy open-air lives, obeying the elementary laws of sanitation, the mortality from tuberculosis would be, if not entirely extinguished, at least reduced to an insignificant figure.

In cattle the disease is very frequent in certain places. From 10 to 20 per cent of all cows shew tuberculosis, the degree of prevalence varying in different parts, and to some extent according to the breed of the cow. Thus in Denmark 31 per cent of cattle were found to react to tuberculin, in Sweden 42 per cent, in Belgium 60 per cent, but in Norway only 8 per cent. In Germany the proportion varies according to locality between 37 and 97 per cent. The Berlin slaughter-houses recorded in 1899 a proportion of rather less than 20 per cent of tuberculous animals. Among cows alone in Saxony the ratio increases with the age of the animals, 99 per cent of all those over four years exhibiting some tuberculous lesion. In Japan tuberculosis is rare among cattle, though common among mankind. Disease of the udder is not a very common manifestation, occurring in perhaps 1·5 per cent of all infected animals (Dollar). Pigs come far behind cattle in their susceptibility to natural tuberculosis. Out of 336,972 pigs slaughtered in Saxony in 1891 (a country in which bovine tuberculosis is very frequent) only 0·28 per cent

were tuberculous. In Copenhagen, however, the percentage of tuberculous swine was 15·8 in 1890-93, and in Berlin 1·55 in 1892-93. In Glasgow (1904) 4·24 per cent of pigs were found to be tuberculous. In the Netherlands (1903-4) the proportion was 1·5 per cent, and in some parts of Germany a percentage of 5·79 was recorded (Buchanan).

In Saxony, out of 85,701 sheep slaughtered in 1891, 30 were tuberculous, or 0·035 per cent. In Copenhagen the percentage (1890-93) was 0·0003, and in Berlin (1892-93) 0·0003. Horses very rarely contract tuberculosis, and dogs and cats still more rarely. Goats are not immune to the disease—a point of some importance, seeing that their milk is not infrequently used for feeding infants. Eichhorn found that in a herd of twenty-eight, nineteen animals reacted to tuberculin. The domestic carnivora—dogs and cats—vary somewhat in this respect. An adult dog will resist the subcutaneous injection of an amount of tuberculous material which would produce generalised tuberculosis in a rodent or in a cow; no local lesion is produced in the dog, which retains its health. On the other hand, tuberculosis can be transmitted to dogs by the intravenous or intraperitoneal injection of a large quantity of bacilli. Similar remarks apply to adult cats; but kittens are readily infected by the disease, either by inoculation or by feeding with tuberculous material. Of all the domestic animals, therefore, carnivora shew the greatest resistance to the development of tuberculosis experimentally. A still greater immunity is possessed by the Algerian rat, already referred to. This animal, although it does develop tuberculosis after inoculation, lives for seven or eight months; and when killed and examined, well-marked retrogressive changes are found in the tuberculous lesions. The resistance exhibited by fowls against the inoculation of human tuberculous material has been pointed out. It is also difficult to produce a generalised tuberculosis in guinea-pigs by avian tuberculous material, although this difficulty does not exist in rabbits.

Mechanism of Immunity.—It is evident from what has been said that the question of immunity is as difficult of explanation in tuberculosis as it is in any other disease. The nature of the disease suggests that the tissue-cells play an important part in the conflict with the bacilli, and Behring's researches support this opinion. On the other hand, Metchnikoff emphasises the work done by leucocytes in devouring the bacilli (phagocytosis), and Sir. A. E. Wright's researches on Opsonins (*vide* p. 139) have thrown a gleam of light upon this factor in immunity. Tuberculous persons may possess in their blood either more or less opsonins than normal individuals. How far this phagocytic process represents the essential factor in immunity is yet uncertain, but the opsonic index appears to run parallel with the agglutinative power of the serum, and to constitute a measure of the resistance of the individual.

Artificial Immunity.—Attempts to increase the resistance of susceptible animals to tuberculosis, by means of inoculation of the bacilli or of their products, have been made by many workers in the field of bacteriology.

Thus, Koch has claimed to produce immunity by injections of his tuberculins and of an emulsion of the bacilli, Behring by inoculation with the substance of bacilli which have been deprived of their toxic properties by extraction with ether and other reagents. Moeller and Friedmann have immunised guinea-pigs by injection of bacilli derived from cold-blooded animals; and in cattle some degree of immunity is produced by inoculation with human bacilli. On account of the risk involved, few attempts have been made to create artificial immunity in man, except by Koch's preparations; but Maragliano has injected dead bacilli subcutaneously, and asserts that he has produced increased resistance by this means; and Klemperer has inoculated himself and others with living bovine bacilli without further ill effects than a local sore. Calmette and Guérin find that oral administration of dead bacilli is capable of producing immunity in animals; and suggest that children might be similarly protected; and v. Behring has recently (1905) held out hopes that his preparation ("tulase") may be applicable to mankind, but the details are not yet published.

The etiology of tuberculosis is centred round the *Bacillus tuberculosis*; where this does not enter the body no tuberculosis can be manifested, and the other diseases, which have just been considered, only dispose to the reception and implantation of the micro-organism from the environment.

Although tuberculosis is most frequent between the ages of fifteen and twenty-five years, it may occur at any *period of life*. It is said, indeed, that at every age-period the ratio of deaths from consumption to the total number of persons living at that age remains curiously constant (T. D. Lister). In rare instances tuberculosis may be congenital —passed on, that is, from the mother to the fœtus when the mother is tuberculous and the placenta is affected. In childhood and adult life the disease is always an infection, but may be influenced in some cases by an inherited condition of body. How far *heredity* conspires in the production of tuberculosis it is impossible to say. Several members of a family, the offspring of tuberculous parents, may exhibit the disease, but this is no strong argument in favour of the inheritance of what has been called the "tubercular diathesis"; if members of a family live together and die off successively, the family is constantly surrounded by infective material, the danger of which is unappreciated: it may well be, then, that many cases of so-called heredity are only cases of infective surroundings. Nevertheless, noteworthy instances occur in which many members of a family scattered over the world succumb to the disease, so that some special susceptibility appears to exist in particular human stocks. In determining the question of heredity, not only must inherited defects in the structure of the thoracic walls, of the lungs themselves, and of the heart be taken into account, but also the mode of life, and the influence of surroundings on the individual.

Tuberculosis is a disease which affects the *sexes* equally. *Pregnancy*, in some instances, delays the progress of the disease, which, however, often increases rapidly after confinement, because lactation is beyond

the powers of the patient. *Climate* and conditions of *soil* have but little influence on the development of tuberculosis, although drainage has been shewn to have an influence on the mortality from the disease (Buchanan).

Some of the principal factors in undermining the natural resistance of mankind to tuberculosis can be readily indicated.

The effect of alcohol on the body must be one of these, since in those suffering from the abuse of alcohol tuberculosis is not an uncommon disease, and runs a rapid course. Syphilis is another disease which diminishes the resistance to tuberculosis; and also diabetes, in which tuberculosis is not uncommonly the cause of death. In cancer, of whatever part, a tuberculous lesion in the lungs is very common. Obsolescent or retrograde tubercle in the lungs occurs in about nine per cent of all necropsies, and of these cancer occurs in by far the largest proportion. In Dr. Fowler's statistics they form about two-fifths of the cases, and in Dr. S. Martin's about two-sevenths. These statistics were obtained from the Middlesex Hospital, where a large number of cases of cancer die every year. In Heitler's statistics, obtained from the Pathological Institute of Vienna, the proportion of cases of obsolete tubercle found in cancer was one-seventh of all cases examined post mortem. In cancer pulmonary tuberculosis is rarely in an active state, but is almost always retrograde; and considering its frequency, it may be said that, although the condition induced by cancer tends to the invasion of the body by the tubercle bacillus, it is not favourable to the spread of the disease.

Congenital malformation of the heart, especially stenosis of the pulmonary artery, is a potent disposing cause of tuberculosis of the lungs. Mitral stenosis, on the other hand, is said to co-exist very rarely with such affection, but it is certainly not an absolute bar to the occurrence of consumption.

Conditions of diminished resistance to the disease are also observed in individuals who may be said to be generally non-resistant to infective disease; those, for example, whose bodily health is diminished by worry and excessive work, insufficient exercise, life in a close atmosphere, irregular or insufficient food; those who inherit from their ancestors a certain weak condition of body, and those who are readily affected by changes of temperature or by changes in mode of life.

There can be little doubt that previous injury to a part is in some cases favourable to the invasion of the tubercle bacillus; but the kind of injury is difficult to specify. In the case of pulmonary tuberculosis the disease not infrequently appears after measles and whooping-cough, in both of which catarrh of one or other part of the respiratory tract takes place. Similarly, the inhalation of certain kinds of dust (vegetable, animal, or mineral), by inflicting an injury on the lung, may be considered to dispose to pulmonary tuberculosis. But this agency, again, is extremely difficult to determine, inasmuch as if dust be inhaled, as it usually is, in the company of fellow-workpeople, and not

uncommonly in a close atmosphere, it is just as possible that the inhalation of dust is not simply the ingestion of metallic or other particles, but also dried sputum which has come from a consumptive fellow-worker; so that the question would not be one of previous injury to the organ affected, but one of direct infection.

Pathological Diagnosis.—The pathological diagnosis of tuberculosis depends partly on the structure of the tuberculous lesion, and partly on the distribution of the lesions in the person or animal affected. As regards the anatomy, there is, with the exception of the presence of the bacillus, no element in the structure of the tuberculous lesion which is diagnostic of the disease. Thus, the presence or absence of the epithelioid cells is not a characteristic of tubercle, nor is the presence of giant-cells. Epithelioid cells may be absent from a tuberculous lesion; and giant-cells, although more numerous in tubercle than in other lesions, are found normally as osteoclasts in bone which is being absorbed, and also in other chronic inflammatory conditions, such as syphilis, in nodules formed round foreign bodies, and in some forms of sarcoma. Necrosis of the central part is not characteristic of the tuberculous lesion, as this may occur in cases where a mucous membrane or an organ is invaded by other forms of cocci and bacilli. This bacterial necrosis is frequently observed in animals, and has been observed in man: it is characterised by the presence in the part affected of whitish or whitish-yellow nodules microscopically consisting of a round-celled infiltration—a leucocytic infiltration, that is—which undergoes necrosis in the central part in practically the same manner as in tuberculosis. The name "pseudo-tuberculosis" has been applied to such conditions as closely simulate tuberculous formations. Small nodules, with or without central caseation, may be caused by the glanders bacillus, by a special organism (*B. pseudo-tuberculosis*), by some varieties of streptothrix, by the mould *Aspergillus fumigatus*, and by certain forms of yeast. In sheep and pigs nematode worms (*strongylus*) give rise to nodules in the lungs resembling tubercles. The lesions caused by the ray-fungus (*actinomyces*) also present some likeness to tuberculous infiltration and excavation.

That which is absolutely distinctive of a tuberculous lesion, and distinguishes tuberculous necrosis from other forms of bacterial necrosis, is the presence of the bacillus tuberculosis; if the tissue be stained in the manner directed and the bacillus found, the lesion is tuberculous. The presence of other acid-fast bacilli only rarely gives rise to difficulties in diagnosis; but in lesions of the urinary organs the smegma bacillus may be a cause of error, and occasionally similar organisms have been found in sputum and in the pus from abscesses. As a rule, these bacteria are decolorised by treatment with absolute alcohol, and they are less resistant to strong acids (30 per cent) than the true *B. tuberculosis*. Inoculation of animals will satisfactorily establish the nature of such organisms. A mixed infection may occur: that is, there may be a tuberculous infection producing its characteristic lesion, and, in addition, an infection by other forms of bacteria—for example, streptococci; in

this case both the bacillus tuberculosis and the other forms of bacteria are found in the necrosed tissue and among the leucocytes surrounding it.

The second point by which tuberculosis may be diagnosed is the distribution of the lesions. Although the distribution varies in individual cases, as the tuberculosis is localised or becoming generalised, yet in every case there is evidence of infection. For example, taking the local tuberculosis of the lungs as it occurs in man, there is the older lesion at the apex of the lung, and, spreading from this towards the base of the lung, there are numerous recent lesions in the form of the granulomas which are diagnostic of the disease. Again, in ulceration of the intestine, it is not so much the transverse direction of the ulcers and their occurrence in the lower part of the ileum which establish the diagnosis, as the presence of miliary tubercles in the base of the ulcer or beneath the peritoneal coat. And so with the other forms of local tuberculosis.

Symptoms of Tuberculosis.—It is difficult to describe the symptoms of tuberculosis as a disease, inasmuch as they are complicated, and frequently obscured, by the special symptoms which arise when tuberculosis affects an important part. In common with other infective disorders it is a febrile disease, and it is known from experiment that it has a period of incubation. This is not observable in man, inasmuch as the lesions of tuberculosis, giving rise to few symptoms and physical signs in the early stages, are not discoverable till some time after they are formed.

As regards symptoms, tuberculosis may be described as a chronic febrile disorder, associated with wasting and frequently leading to death. The fever varies greatly. In rapid and advancing cases it may be high and continuous for a long period. In cases which advance less rapidly it may be a typical hectic fever, with an evening rise and morning fall. All variations between hectic and continuous fever are observed. In more chronic cases (and these are the most important, because of the difficulty in their diagnosis) as well as in the early stages of cases in which there is great resistance to the invasion of the disease, the fever becomes irregular: there is at no time high fever, and there may be periods of complete remission; but the long continuance of the fever leads to the suspicion of tubercle. Tuberculosis in this respect forms a marked contrast to cancer. The fever is associated with wasting, which is frequently out of all proportion to the degree of it; and is most pronounced in cases in which an important organ, such as the lungs, is affected, or when—as in tuberculous peritonitis and enteritis with much glandular affection—the absorption of food is interfered with. The fever in all forms of tuberculosis is frequently accompanied by night-sweats, occurring in the early morning, when the temperature begins to fall. The sweating at night also is usually out of all proportion to the degree of fever, and is then due to the general condition of the patient. It is, however, difficult to determine how far the sweating is due to the action of pyogenetic organisms which gain a footing in the tuberculous lesions.

Besides these symptoms, tuberculosis is apt to produce anæmia, and

also exercises a profound effect on other organs of the body. Fatty change in the heart, liver, and kidneys is observed in advanced cases. Lardaceous change in the spleen, kidneys, liver, stomach and intestines, and gastric catarrh, with functional disorders of intestinal digestion, may also be present.

Into the *physical signs* of the different forms of local tuberculosis and their special symptoms it is not necessary to enter here, as they are fully described elsewhere; but it may be remarked that the severity of the general symptoms of the disease depends upon the chronicity or acuteness of the spreading tuberculosis; with very chronic lesions there are but few general symptoms, since the extensive fibrosis around the chronic lesion shuts it in, preventing absorption of the toxins which produce the general symptoms. In the acute lesion, on the other hand, the poisons, being rapidly absorbed, produce severe constitutional symptoms. Other factors necessarily play a part in producing the severity of the symptoms, namely, the general condition of the patient and the presence of disease elsewhere in the body.

Diagnosis.—The diagnosis of localised tuberculosis depends upon a combination of signs pointing to disease affecting a particular organ, with the general symptoms already described—wasting, irregular fever, and night-sweats. Absolute confirmation of the suspicions thus aroused is only obtainable by the discovery of the tubercle bacillus in the discharges from the lesion or in portions of tissue removed for examination. The recognition of tuberculosis affecting the different organs of the body is discussed in detail in special articles in this *System*. Here it is only necessary to allude to certain tests applicable to all forms of the disease alike, and to a few morbid conditions which may arouse a suspicion of the existence of some deeply seated focus of tuberculosis without localising symptoms.

It is now generally recognised that Koch's (old) *tuberculin* affords valuable assistance in the diagnosis of latent tuberculosis. In the disappointment which followed the exaggerated hopes excited at the time of its introduction, undue fears were excited as to the dangers incurred by injections of this substance, many authors maintaining that an acute outbreak of tuberculosis was liable to follow this procedure. Further experience in the use of tuberculin has shewn these fears to be unfounded, provided that reasonable precautions be adopted in administering the drug. Small doses should be employed for the first injections ($\frac{1}{10}$ to $\frac{1}{2}$ milligramme); these may be raised to a maximum of 5 mgr. in the course of ten days or a fortnight if no reaction occur with the smaller amounts. The course of the patient's temperature must be observed for some days before the tuberculin is administered, as it is not advisable to make use of the test in cases which already exhibit a range of fever rising to 100° F. A "positive" reaction is manifested by a rise of temperature amounting to 2·5° F. This generally occurs in about eight to twelve hours after the injection, and quickly subsides, but some febrile disturbance may remain for the next two or three days. The test is not infallible, as a reaction occurs

now and then in persons who have no tuberculous infection, especially in syphilitic subjects. It appears, however, to be correct in at least 95 per cent of cases. It must be borne in mind that a reaction does not necessarily prove the specific nature of any particular focus of disease; for example, if an injection be administered to clear up the diagnosis in a case of arthritis, the presence of tuberculous mediastinal glands may determine a reaction, although the articular lesion is not tuberculous. In such a case signs of additional inflammation might be expected to occur in the affected joints if they were the seat of tuberculosis. The injection of tuberculin is followed by some symptoms of constitutional disturbance —headache, pains in the limbs, and nausea—as well as often by a slight degree of local inflammation at the site of administration. Koch recommends the skin of the back for this purpose, but the position is immaterial.

It has recently been suggested that a study of the opsonic index (p. 139) of the blood may be used for diagnostic purposes, a minute injection of (new) tuberculin being followed in a tuberculous subject by a fall in opsonic power, whereas this phenomenon does not occur in a healthy person. Further observation is necessary to determine the value of this suggestion; in any case the test is one which can only be carried out by an experienced observer.

Various methods have been suggested for the recognition of tuberculous serous effusions. Thus it is found that the cells which they contain are almost entirely lymphocytes, as contrasted with more acute inflammatory fluids in which polymorphonuclear leucocytes predominate (*cyto-diagnosis*). This test is of most value in the case of pleural effusions: in the cerebro-spinal fluid the same peculiarity occurs, but it may also be met with in other chronic conditions, such as tabes dorsalis and syphilitic meningitis. For the discovery of tubercle bacilli in inflammatory fluids it has been recommended that coagulation should be induced and that the clot should then be artificially digested: by spinning the resulting solution on a centrifuge the bacilli are separated and readily found in stained preparations of the deposit (*inoscopy*, Jousset). The value of this procedure is disputed. Failure to find any organisms in an inflammatory effusion is presumptive evidence of its tuberculous nature, since the bacteria responsible for other forms are usually present in sufficient quantities to be readily discoverable. Injection of the fluid into susceptible animals (guinea-pigs) may prove the presence of tubercle bacilli when these are not discoverable with the microscope.

All conditions which give rise to chronic irregular pyrexia without definite localising signs may excite suspicion of the presence of a deeply seated tuberculous focus. Of these we may mention enteric fever, Malta fever, syphilis, infective endocarditis, septicæmia and pyæmia, osteo-myelitis, and other deep suppurations. The diagnosis from enteric fever and infective endocarditis is considered on p. 299.

In *Malta fever* there is a gradual invasion with headache and lassitude. The fever is remittent or intermittent. There is slight cough and often

profuse sweating; the liver and spleen may be enlarged and the abdomen somewhat distended. The resemblance to generalised or to pulmonary tuberculosis is often very close. Residence in an infected locality will, however, suggest Malta fever, and the agglutinative power of the patient's serum upon the *Micrococcus melitensis* will establish the diagnosis.

Syphilis in the secondary stage may give rise to prolonged fever without the presence of a rash or other characteristic evidence. A history of infection and the rapid efficacy of mercurial treatment will soon remove any doubt as to the nature of the condition.

Deeply seated *collections of pus* or absorption of poisonous products from some latent ulcerated surface—for example, in the nasal passages—may lead to febrile disturbance, which in the absence of discoverable physical signs may give rise to a suspicion of tuberculosis. Thus, in old cases of otitis media chronic fever may be produced, either by retention of purulent discharge due to granulations in the external auditory meatus or as the result of caries of the bones surrounding the internal ear, with or without meningitis. Encysted empyema and pelvic abscess are other instances of conditions which may simulate tuberculosis. In all such cases an examination of the blood is likely to shew a higher degree of leucocytosis than usually accompanies tuberculous infection. In children an infective pyelitis may give rise to continued intermittent pyrexia; the affection is signalised by the appearance of small quantities of pus in the urine without accompanying tubercle bacilli. In osteo-myelitis careful examination will reveal some swelling and tenderness, as well as some loss of mobility in the affected limb. In puerperal women latent uterine sepsis may give rise to a suspicion of tuberculosis, and the converse error may also occur, consumption being mistaken for uterine trouble. A vaginal examination will usually clear up the doubt in these cases.

The diagnosis of tuberculous glands from lymphadenoma, of tuberculous peritonitis from other causes of ascites, and of tuberculous meningitis from affections due to the meningococcus or to other organisms, is discussed elsewhere.

Prognosis.—The prognosis in tuberculosis depends in the first place on whether the disease is generalised or confined to a single focus. Generalised tuberculosis is probably always fatal. In localised affections the outlook varies with the importance of the organ attacked, with its accessibility to surgical treatment, and above all with the signs by which we are enabled to judge of the resistance of any individual patient. The circumstances of the sufferer—his ability to adopt all possible means of cure, to obtain nourishing food, to give up an unhealthy occupation, to select a residence in a suitable locality, as well as his family history, his temperament, and his apparent condition at the time when he comes under observation—all these factors have to be taken into consideration. Signs of a rapidly extending lesion are seen in loss of appetite, high fever, progressive emaciation, and loss of strength. A red tongue partly coated with thick fur is usually indicative of active disease.

Regarding the special prognosis of individual local lesions little need

be said here. In tuberculous glands of the neck the outlook is as a rule good. The disease sometimes spontaneously heals; in other cases operative procedure leads to a cure. In some of these cases, however, the disease spreads down the glands of the neck and affects the lungs: all such cases are of serious import. In primary tuberculosis of the intestines, with or without infection of the peritoneum, the disease sometimes becomes localised and heals. This occurs not infrequently in children. In many cases of primary tuberculous peritonitis, in which there is not extensive ulceration of the intestine, the disease remains localised, chiefly because the progress of the lesion being slow, a large amount of fibrosis occurs, which blocks up the lymphatics leading from the peritoneal cavity, and so prevents the absorption of the virus, and thus the dissemination of the disease. On the other hand, from the intestine the disease may spread to the lungs and other parts of the body; all such cases are very serious. Simultaneous infection of two localities, as of the peritoneum and pleura, is of unfavourable import, and signs of secondary extension of the infection—for example, of tuberculous laryngitis or enteritis in pulmonary disease—are especially grave.

Primary tuberculosis of the lungs is serious according to the extent of the local lesion and to the indications of actively extending disease: in the majority of instances general infection does not occur until the later stages. Prognosis depends, then, on the condition of other organs; as, for example, when there is fatty degeneration of the liver and kidneys, or lardaceous change in the organs, or severe gastric catarrh. All such cases are grave. Tuberculosis of the kidney leads to complete destruction of a vital organ; and although usually more advanced in one kidney than in the other, the disease is not uncommonly bilateral. Tuberculosis of bones, of joints, and of the epididymis, when existing alone, is serious according to the results of surgical treatment, according to the signs of the dissemination of the disease, and the presence of the various forms of secondary degeneration of other organs. The symptoms and signs of generalised tuberculosis, occurring in any form of local tuberculosis, are always perilous, and usually end rapidly in death.

Treatment.—Many attempts have been made to discover a specific remedy for tuberculosis. Allusion has already been made to protective inoculation (p. 288). Koch introduced both the old and the new tuberculin as remedies for the disease, hoping by their use to strengthen the resisting power of the tuberculous patient. He has made use of his emulsion of bacilli with the same object. On the whole, the results recorded from the use of the *new tuberculin* (TR) are sufficiently favourable to warrant a cautious use of this preparation, in addition to recognised hygienic measures. Very small doses should be used at the beginning of a course of treatment ($\frac{1}{1000}$-$\frac{1}{500}$ mgr.), and it is advisable, in accordance with Sir A. E. Wright's advice, to be guided by the opsonic index of the blood in determining the frequency of the injections. Each dose is followed by a temporary fall in opsonic power, which subsequently rises to a point higher than that previously existing; a second dose should not be

administered till this rise has occurred. Only chronic cases are suitable for this treatment, which should be begun as early in the disease as possible.

The *old tuberculin* is sometimes of use in the treatment of superficial tuberculosis (lupus), but relapse often takes place on discontinuing the injections.

Klebs has introduced modifications of tuberculin for purposes of treatment, under the names of *tuberculocidin* and *antiphthisin*; the former is prepared from tuberculin by precipitating certain albuminoids by means of bismuth sodic-nitrate, removing the bismuth and precipitating by alcohol from the remaining fluid a substance which is said to possess curative properties without the pyogenetic and toxic qualities of tuberculin. Antiphthisin is prepared from bacterial cultures without heat, but is otherwise very similar to tuberculin. Neither of these remedies has been at all extensively used in this country, and their value remains uncertain.

Several other modifications of tuberculin have been introduced. Thus, v. Ruck devised a preparation called *tuberculinum purificatum*, formed by heating the bacilli and their culture-fluid in a vacuum for long periods of time at a temperature of 120°-130° F. He also made trial of a watery extract of bacilli, which were first deprived of fat by extraction with ether, then dried, triturated, and extracted with distilled water at a temperature of 120° F. Some good results have been ascribed to these remedies, but they have not gained general acceptance. Hirschfelder devised a substance known as *oxytuberculin*, which received favourable comment at the time of its introduction, and Beraneck has prepared a special tuberculin by mixing the toxins formed in the culture-fluid with those derived from the bodies of the bacilli themselves. It has not been shewn that any of these modifications are superior to Koch's original tuberculins.

Antituberculous serums have been prepared by Maragliano and by Marmorek. Good results are claimed for the use of *Maragliano's serum* in Italy, but it has not gained acceptance elsewhere. The value of *Marmorek's serum* is still doubtful. It is certainly not an inert substance, and sufficient indications of a remedial action have been observed by some of those who have used it to render it worthy of more extended trial.

Some benefit has appeared to result from the employment of *antistreptococcic serum* in cases in which the presence of large numbers of streptococci in the sputum indicates the existence of a secondary infection of tuberculous cavities by pyogenetic organisms.

Link found that benefit resulted in animals from oral administration of the serum of the dog—a resistant animal; and Mr. Montgomery Paton advises the use of the plasma of immune animals, attributing to this substance a stimulating action on the cells of the tissues. Possibly the administration of raw meat (*zomotherapy*), which has been lauded for the treatment of tuberculosis, may be proved to owe whatever merit it possesses to this mode of action.

Certain drugs have been stated to exert a specific action on tuberculous lesions. Of these, preparations of *cinnamic acid* (hetol) are supposed to act by increasing the number of leucocytes in the system, and thus facilitating the process of phagocytosis; the value of the remedy is problematical, but it is probably not injurious.

Urea has been administered to tuberculous patients—a synthetic product being employed—on the ground that carnivorous animals are immune to tuberculosis and that gouty persons are seldom infected, their resistance being ascribed to the amount of urea and uric acid which they have in their systems. The idea underlying the treatment is probably erroneous, and urea itself is practically inert, with the exception of a certain degree of diuretic action.

Calcium chloride and *carbonate* have been recently recommended on grounds more ingenious than convincing ["Recalcification," Ferrier].

In localised tuberculous lesions, *e.g.* arthritis, attempts have been made to combat the disease by inducing a condition of *passive hyperæmia.* For this purpose elastic bandages are passed round the limb above and below the affected joint, thus restricting the local circulation. It has been suggested that the rarity of pulmonary tuberculosis in patients suffering from mitral stenosis is due to the chronic engorgement of the lungs which is present.

The value of *fresh air* in the treatment of all forms of tuberculosis is well established; indeed it is desirable that every case of the disease, whatever the localisation of the lesion, should be treated, if possible, in the country or at the seaside. The value of sanatorium treatment will be discussed in a later volume of this *System.* Here we need only point out that very good results may be obtained under home conditions by patients who are able and willing to carry out faithfully and intelligently an open-air course of life. Plentiful feeding is another essential factor in treatment; but the great importance of keeping the digestive system in good order sufficiently negatives the advisability of such forced feeding as was at one time deemed essential. The special treatment called for in the various forms of tuberculosis is discussed in the articles dealing with diseases of particular organs.

Acute Generalised Tuberculosis

Acute general tuberculosis, or acute typhoid tuberculosis as it is sometimes called, is best termed acute generalised tuberculosis. As has been fully explained in discussing the pathology of the disease, it may occur in two chief forms, in one of which there is a generalised tuberculosis of the body directly following infection; in the other, after the persistence of a chronic lesion for some time, a generalised tuberculosis proceeds from it. Clinically the two classes of cases are very similar, and the nature of the latter event may not be understood until on post-mortem examination a chronic lesion of the lungs or intestine, too small to have given rise to physical signs, is revealed. Indeed, a primary acute

generalised tuberculosis is probably not met with in man, as it is practically always possible to demonstrate post mortem a caseous gland or other source of infection. The bacilli are distributed throughout the body by the blood-stream, due either to ulceration of a caseous focus into a vessel or to tuberculosis of the intima. Infection of the receptaculum chyli and thoracic duct may also lead to generalised tuberculosis—a factor, the importance of which has recently been emphasised by Longcope, who found, among nineteen cases of acute generalised tuberculosis, fourteen in which there was disease of the thoracic duct.

The symptoms of acute generalised tuberculosis are those which have been discussed already, but they are accentuated. Thus the illness may begin acutely, and progress with high fever, night-sweats, great emaciation, and bodily prostration, until the patient sinks into the typhoid condition which precedes death. In other cases, perhaps in the majority, the onset is insidious, like that of enteric fever, which is closely simulated in course and symptoms (*typhoid type*). The fever is usually remittent or intermittent in character, rising to a high degree in the evening and falling in the morning; occasionally the *typus inversus* is met with, the highest point being attained in the morning. Cases also occur in which the course of the disease is almost apyrexial.

It is characteristic of acute generalised tuberculosis that with these severe symptoms there are but few signs of the local affection of organs. Thus, although the lungs may be found studded with tubercles after death, the cough is but slight, or dry and hacking only, and without hæmoptysis; there is no pus in the urine (unless the kidneys were previously affected with chronic tuberculosis); there is no diarrhœa referable to the disease, inasmuch as any looseness commonly occurs towards the end of the illness, and is part of the "typhoid" condition. The heart presents no abnormal sign. Enlargement of the spleen may be discovered, but the splenic enlargement in acute tuberculosis is never great, and does not often give rise to a characteristic tumour in the left hypochondrium. Cerebral symptoms may supervene, perhaps early in the disease (*meningeal type*), headache and slight delirium with crying out. These symptoms are not definitely characteristic of tuberculous meningitis unless combined with retraction of the head, slowing of the pulse, ocular palsy (seen either in the pupils or as slight strabismus), or with the presence of tubercles in the choroid, when tuberculosis of the pia mater becomes evident. In other instances signs of pulmonary involvement are present in the form of dyspnœa and cyanosis; this variety (*pulmonary type*) is common in young children who suffer from generalised tuberculosis as a sequel of measles or whooping-cough.

Morbid Anatomy.—Almost every organ of the body may be found studded with minute granulomas. The lungs usually suffer most, but the kidneys, liver, and spleen exhibit a larger or smaller number of grey points, and even more minute lesions are discoverable with the microscope both in these and in other organs. In the meninges of the brain the tubercles are most readily detected by floating the pia mater in water

over a dark background. The base of the brain is most affected, but minute granulomas may be seen following the course of the vessels in the Sylvian fissures. There is usually some turbid fluid at the base of the brain, while the convolutions are dry, sticky, and somewhat flattened. The primary focus of tuberculosis may need careful search, as it may exist in bone or other deeply seated part. Affection of the intima of the pulmonary vessels is present in many cases (Weigert, Silbergleit), giving rise to a constant supply of bacilli in the circulation.

Diagnosis.—Acute generalised tuberculosis must be distinguished from other febrile disorders associated with wasting and irregular pyrexia. The difficulty in the diagnosis lies in the indefinite character of the physical signs.

Enteric Fever.—In this disease, as in tuberculosis, there are headache, delirium, slight bronchitis, and enlargement of the spleen. In both alike the diazo reaction of Ehrlich may occur in the urine. In generalised tuberculosis, however, which is rare in persons over twenty years of age, and most common in young children—the latter being seldom affected by typhoid,—diarrhœa and tympanites are uncommon, the mental condition is clearer until signs of meningeal invasion occur, and the pulse is much more frequent than is usual in enteric fever. The presence of scars of tuberculous abscesses in the neck, of a healed lesion at the apex of the lung, of tuberculous joint-disease or epididymitis, is suggestive of tuberculosis; so, too, is the occurrence of distinct dyspnœa or cyanosis. The occurrence of "rose-spots" strongly suggests, but is not absolute proof of, the presence of enteric fever (*vide* Vol. I. p. 1137). The most important diagnostic sign of the latter is afforded by the occurrence of the "agglutination reaction" in the blood. As a "counsel of perfection" it may be recommended to perform the test, if negative with *B. typhosus*, with the two varieties of paratyphoid bacillus also, before excluding this type of infection. Opinions differ as to the value of the corresponding reaction with tubercle bacilli (Arloing and Courmont), but in doubtful cases a trial of this test would seem advisable. The blood in generalised tuberculosis is likely to exhibit a polymorphonuclear leucocytosis, as opposed to the leucopenia of enteric fever.

Infective (malignant) Endocarditis.—In certain cases diagnosis between acute generalised tuberculosis and infective endocarditis may be difficult. If in such a patient the evidence of a chronic tuberculous lesion be known, the symptoms (fever, wasting, and prostration) may be ascribed to a generalisation of the disease. When no such local tuberculous lesion is evident, difficulties arise, inasmuch as infective endocarditis is a disease of many aspects: it consists in an acute affection of the heart, with multiple embolism and with enlargement of the spleen; and thus, if one or more cardiac murmurs be present, and especially if one or more of these vary in character from day to day, or again, if there be a persistent or loud pulmonary murmur, or if there be evidence of embolism, such as a sudden hemiplegia, a thrombosis of arteries of a limb, hæmoptysis (due to infarction of the lung), hæmaturia (due to infarction of the

kidney), or severe pain in the left hypochondrium, with more or less sudden enlargement of the spleen, the case may be clear from the first as one of infective endocarditis. Yet, at one period of infective endocarditis cardiac murmurs and the signs of embolism may be absent, and no diagnosis may be possible until the occurrence of embolism on the one hand, or of local lesions characteristic of tuberculosis (such as meningitis) on the other, dispel our doubts. An examination of the blood may aid in the diagnosis of the cardiac affection, since the causal organisms may at times be cultivated, and leucocytosis is likely to reach a higher degree than in tuberculosis.

Prognosis.—The outlook in acute generalised tuberculosis is, in the present state of medical knowledge, hopeless, death occurring after a period of six weeks to three months.

Treatment.—The use of a serum, such as Marmorek's, would seem rational treatment for acute tuberculosis, but unfortunately the results so far obtained from its use in this form of the disease are disappointing. The remedy should be administered early, if at all. Apart from this, all that can be done is to support the patient's strength by food and stimulants, and to relieve any urgent symptoms that may arise.

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W. C. B.

THE PATHOLOGY OF STREPTOTHRIX INFECTIONS

By Alexander G. R. Foulerton, F.R.C.S.

The use by pathologists of a somewhat varied nomenclature for the designation of the species of vegetable pathogenetic parasites here described under the generic name of Streptothrix has been the source of some confusion in the nomenclature of the diseases caused by this kind of organism. But since a full historical account of the diseases thus caused is given by Dr. Acland in his article on "Actinomycosis," it will only be necessary to refer here to the literature of the past in so far as this will be of use in clearing up any remaining confusion.

The name Actinomycosis was applied by Bollinger (1877) and by Israel (1878) to a form of disease occurring in cattle and in man, which was believed to be the result of infection by a single vegetable parasite, the Ray-Fungus (*Actinomyces bovis* Harz). During the next twelve years or so a number of cases of actinomycosis in man and cattle were observed and recorded in this country and elsewhere; the first human case positively identified in England was investigated by Dr. Acland in 1884. In Dr. Acland's case the liver was affected; the first example of pulmonary infection in this country was recorded in 1889 by Sir R. Douglas-Powell and Mr. Godlee. During this period the diagnosis of the disease was completed by the identification of an organism of the ray-fungus type in the tissues affected and in various discharges; the parasites were not isolated in pure culture and studied, and differentiation of species was therefore not possible. Indeed the identity of the ray-fungi occurring in all cases of actinomycosis both in man and in cattle was assumed in papers published in this country by Prof. Crookshank and Sir John M'Fadyean as late as 1889.

In 1890 Bostroem published a fairly full account of the biological characteristics of some ray-fungi which he had isolated from cases of human and bovine actinomycosis, and which he regarded as belonging to one and the same species. In 1891 Wolff and Israel published a similar account of a different species of ray-fungus isolated from a case of actinomycosis in man; and since then a considerable number of species, some presenting well-marked specific characters, and others but ill-described and not clearly differentiated as belonging to separate species, have been referred to under the generic name Actinomyces and as occurring in cases of actinomycosis. The name Streptothrix was probably first used by Corda in 1834 as a designation for a species of hyphomycetes or mould-fungi, but at the present time it is not certain what particular organisms the term was applied to. In more recent times Cohn (1874) applied the name Streptothrix to an organism (*S. foesteri*) found in concretions from the lacrimal canal, which probably belonged to the

class of organisms for which the name is used at the present time. In 1888 Macé published a careful biological account of a saprophytic organism of a branching type which Cohn, believing that the ramifying form was the result of a true dichotomy, had previously described under the name *Cladothrix dichotoma.* Macé, however, found that the branching was not produced by a true dichotomy, that is to say by the division of a parent filament into two others of equal size; his observations shewed that the branching resulted from the development of secondary filaments by a lateral budding out from the parent filament, and there seems to be no doubt but that the *Cladothrix dichotoma* of Cohn was in reality a typical streptothrix (*Streptothrix nigrescens* Foulerton).

In 1888 Nocard described an organism, now known as *Streptothrix nocardii* seu *farcinica*, which he isolated from the lesions of a disease termed *farcin des bœufs* which was especially prevalent amongst cattle in Guadeloupe. Nocard gave a full description of the morphology, cultural characteristics, and pathogenetic action of the organism; he surmised that it was a bacillus of a kind that had not been described previously, noting particularly the occurrence of a lateral branching similar to that which Macé had observed in Cohn's *Cladothrix dichotoma.* Nocard's organism has been isolated several times since it was first described, and is now well recognised as the cause of a disease in cattle, with special clinical features which in many cases serve to distinguish it from the more common manifestations of streptothrix infection in cattle, caused by *Actinomyces bovis* Harz (*Streptothrix bovis communis* Foulerton), as it occurs in this country. In 1890 Eppinger isolated an organism which he named *Cladothrix asteroides* (*Streptothrix eppingeri* seu *asteroides*) from a case of multiple abscesses in a man; his description of the parasite was an excellent one, and has enabled the same organism to be identified in several cases since then. In 1891 Rossi-Doria described several saprophytic species of streptothrix which he had isolated from the air. In 1892 Sauvageau and Radais published a valuable monograph entitled *Sur les Genres Cladothrix, Streptothrix, et Actinomyces, et description de deux Streptothrix nouveaux*; they suggested, however, the adoption of Oospora as the generic designation in the place of the three other synonyms. In 1894 Gasparini also dealt at length with the biology of the genus, reverting to the older generic term Actinomyces. In 1894 Vincent isolated in pure culture and described the causative parasite, *Streptothrix maduræ*, occurring in cases of Mycetoma or Madura foot, and compared the organism with *Actinomyces bovis* Harz, as isolated and described by Bostroem. Thus Actinomyces, Cladothrix, Oospora, and Streptothrix have each been used as the generic designation for these parasites; and to the list a fifth name has yet to be added—Nocardia, as suggested by de Toni and Trevisan in 1889. Three of these generic names have dropped out of use during recent years, and we are left with only two, Streptothrix and Actinomyces, to choose between. The former term has now by common consent been adopted generally by British and American pathologists and by many others, whilst Actinomyces is apparently still

used by preference in many parts of the European continent. And since the term Streptothrix has been adopted generally in this country as the generic name for these species of parasites, it would seem that Streptotrichosis, as recommended by a Committee of the Pathological Society of London in 1899, is the appropriate clinical designation of the large class of streptothrix infections. The term Actinomycosis has long since lost its original significance as the name of one specific disease, and can be used only synonymously with Streptotrichosis.

Amongst the more recent monographs dealing with the morphology, general characteristics, and pathogenetic action of these parasites are those of Berestnew (on *Actinomycosis*, 1897), of Lachner-Sandival (*Ueber Strahlenpilze*, 1897), and Foulerton and C. Price Jones (*On the General Characteristics and Pathogenic Action of the Genus Streptothrix*, 1901).

FIG. 1. *Streptothrix melanotica* (C. Price Jones); growth of filaments from spores, after twenty hours (× about 750).

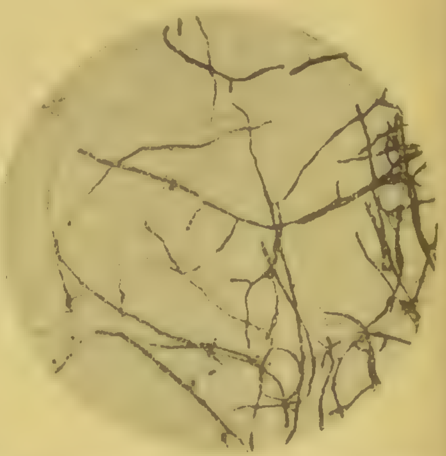

FIG. 2.—*Streptothrix luteola* (Foulerton); from a two-weeks old culture in peptone beef broth, incubated at 37° C. (× about 750).

The Characteristic Morphology of the Streptotricheæ. — The morphology of the streptotricheæ as observed in cultures on artificial media may now be described. If the spores of a rapidly growing species are kept under observation on a warm stage at a suitable temperature, the earlier stages of development may be clearly seen within some eighteen or twenty hours. From the spherical spore two or three small buds project and, gradually elongating, become the primary filaments of the mycelial mass. From the primary filaments lateral branches bud out, and from these secondary branches other lateral filaments again grow out by a repetition of the budding process; and in this manner a more or less dense and tangled tuft of wavy branching mycelium is formed. I have never observed the formation of branches by a true terminal dichotomy. The general characters of the tuft of the adult mycelium are best studied in a culture in ordinary peptone broth, under which condition the mycelium

presents itself usually as a discoid, but sometimes globular, mass of tangled filaments, with a dense central portion and a looser arrangement towards the periphery of the tuft. The termination of the filaments presents various appearances in different species, and the appearance may not be constant in the same species; the end of the filaments may be pointed or rounded off, or may present small spherical or Indian-club shaped enlargements. Up to a certain stage the mass of mycelium consists of filaments of nearly homogeneous appearance; then changes occur which may be described as comprising segmentation and fragmentation of the mycelium and a process of chain-sporulation. The adult mycelium presents a homogeneous appearance when stained with the ordinary basic anilin dyes or by Gram's method; when segmentation occurs there is an alteration in the staining properties, resulting from a degeneration of shorter or longer segments of the constituent filaments occurring at irregular intervals along their length. The degenerated portions of the filaments no longer retain the stain when treated by Gram's method, and stain but faintly with the basic anilin dyes employed in the usual way: in unstained hanging-drop specimens the altered segments present the appearance of a fine cylindrical sheath which has collapsed after the escape of its former contents. Fragmentation of the mycelium follows on segmentation; the degenerated segments gradually disappear, and in the place of the original tuft of branching mycelium there are collections of separate, shorter or longer, lengths of the filaments, which may appear as straight or slightly curved rods, or may retain the wavy outline of the original mycelium, or may present a well-marked corkscrew or spirillum shape. Some of the segments of the mycelium will shew a short lateral branch still attached, they stain well by Gram's method, and often present a beaded appearance. These segments represent more resistant portions of the mycelium, they appear to retain their vitality for a considerable time, and are probably capable of sprouting out into a new mycelium when transferred to a fresh medium without the intervention of a spore-stage. If not transferred to a fresh medium, the majority, at any rate, of these segments die out without undergoing any further change; but it is not quite certain whether or not after fragmentation there may be a process of chain-sporulation in some of the persistent segments. On the other hand, it is quite certain that the rod-segments never give rise directly to new rod-segments by a process which is in any way analogous to the fission-process which is characteristic of the bacillary forms of schizomycetes. Coincidently with the occurrence of segmentation of the mycelium, indications of chain-sporulation may often be seen. The terminal portion of some of the filaments and of their lateral branches assumes a closely-beaded appearance, resulting from a complete transverse segmentation which is probably similar in its nature to that which has been described already as occurring in the length of the filaments. In the terminal portions, however, segmentation occurs at regular and close intervals, and the alternate narrow truncated segments which still stain by Gram's method

gradually assume a spherical or oval shape. The intervening degenerated segments then disappear, and the free spores are seen as isolated spherical bodies which stain well by Gram's method, and which are morphologically and in their staining characteristics indistinguishable from many species of cocci.

The above description applies to the morphology of a streptothrix when growing in a fluid medium, and it will be seen that the appearances are widely different at different stages. At first there is the tangled mass of mycelium which a little later will shew indications of segmentation and chain-sporulation; then when fragmentation is complete there will be found, side by side, isolated rod-segments or longish filaments and spherical spores, and at last the culture will shew only spores arranged in irregular masses like staphylococci, or in pairs, or still retaining their chain-arrangement and indistinguishable from streptococci when stained by Gram's method.

FIG. 3.—*Streptothrix luteola*; from a six-weeks-old culture on maltose agar, incubated at 37° C. (× about 750).

When the organism is growing on a solid medium the same morphological cycle may often be traced; but under these conditions of growth it is also frequently difficult to connect the several stages in their proper order.

In quickly growing species the mycelium usually forms a densely felted tenacious layer which spreads over the surface of the medium, and sends out vigorous lateral branches into its substance. After a time segmentation occurs, followed by fragmentation as when the organism is growing in a fluid medium. In many of the species which have been examined, spores are developed by a process of chain-sporulation occurring in fine aerial hyphæ which grow erect from the surface of the mycelial layer. These aerial hyphæ should be regarded as the special spore-bearing organs of a hyphomyces, and in many species the occurrence of sporulation is usually indicated by the appearance of a chalky kind of efflorescence on the surface of the growth.

In some of the pathogenetic species of streptotricheæ which grow but scantily and very slowly on artificial media, the growth on solid media may be such that it is impossible to trace the complete morphology of the organism as described above. The mycelium develops very slowly, and segmentation and fragmentation of the filaments appear to occur nearly coincidently with growth. In such cases the ordinary cover-glass preparation will shew little more than closely packed masses of rod-segments which often have a beaded appearance, the whole closely

resembling what is seen in a similar preparation from a culture of *B. diphtheriæ* or *B. tuberculosis.* But here and there longer filamentous segments, possibly with the remains of a lateral branch still attached, will be seen; and later on sporulation is obvious. As a rule, when the culture on a solid medium is of this somewhat indefinite character it will be found that typical discoid or globular colonies develop in broth cultures and show the complete cycle of morphological change.

The Place of the Genus Streptothrix in Botanical Classification.—Harz, with much less knowledge of the morphology of these organisms than we now possess, placed Bollinger's ray-fungus amongst the Hyphomycetes or mould-fungi, and the investigations which have been carried out during recent years under much more favourable conditions have but confirmed Harz's opinion. It is true that some pathologists have questioned the correctness of the classification of the streptotricheæ amongst the mould-fungi, regarding the branching mycelium, the rod-segments, and the spherical spores as merely casual morphological variations of a highly pleomorphic fission-fungus, which under different conditions may assume a branching filamentous, a spirillar, a bacillary, or a coccal form. In the majority of cases probably the objection raised to the classification of the streptotricheæ amongst the mould-fungi has been founded on observations made on slow-growing species in which the complete life-cycle is difficult to follow; and a study of the morphology in species in which the sequence of changes can be closely followed leaves very little doubt but that these organisms belong to the moulds under our present system of botanical classification.

No multiplication of the rod-segments as such, or of the spherical spores, ever takes place by a process of fission such as is characteristic of the fission-fungi; the aerial hyphæ represent the specialised spore-bearing organs of a hyphomyces; and the spores of the streptotricheæ, whilst they resemble the spores of other hyphomycetes in their thermic death-point and staining reactions, do not stain by the characteristic Moeller's method which is used for demonstrating the spores of fission-fungi, nor do they correspond with the spores of fission-fungi in respect to their thermic death-point.

Cultural and Staining Characteristics of the Streptotricheæ.—The cultural characteristics of the streptotricheæ can be referred to here in general terms only; for more detailed information the reader should refer to a paper (20) in which a full description is given of the cultural characteristics of nine pathogenetic and sixteen saprophytic species which were examined at the Middlesex Hospital.

Difficulty in the differentiation of species of the pathogenetic streptotricheæ frequently arises because in some cases no growth of any kind can be obtained on artificial media, whilst in other cases only a very scanty growth can be obtained and the organism dies out rapidly when attempts at subcultures on artificial media are made. Certain pathogenetic species, however, grow with considerable freedom on artificial media, and so can be identified readily when met with as the cause of

disease. Excluding cases in which all attempts at obtaining growth on artificial media fail, the streptotricheæ may be roughly divided into three groups in accordance with the general characters of the growth which they yield on artificial media.

In the first group may be placed the organisms which grow with a certain luxuriance on nutrient agar, or nutrient agar containing glucose or maltose. This group includes the majority of the saprophytic species which have been described, and also a number of parasitic and pathogenetic species, such as *Streptothrix bovis communis*, one of the species isolated from disease in man by Berestnew, the species which were similarly isolated by Garten and by Hesse, the three species isolated by the writer—*Streptothrix luteola* and *Streptothrix hominis* III. and IV. Foulerton—and several other unnamed species which have been described by other writers. Amongst this group there are some whose growth is characterised by a "mouldy" or earthy smell, many form pigments, many liquefy gelatin, some liquefy inspissated blood-serum, and some exercise an active hydrolytic action on starch. A noticeable characteristic of one or two species which have been examined is the production of a distinctly feculent smell, especially in broth cultures.

Next there is a small but well-defined group of pathogenetic streptotricheæ which includes a number of "acid-fast" species—*Streptothrix nocardii*, *Streptothrix eppingeri*, *Streptothrix capræ* (Silberschmidt), and the organisms described by Sabrazès and Rivière. *Streptothrix maduræ* (Vincent) may be classed with these because of its general characters, although the cultures of this organism which the writer has examined have not shewn any indication of acid-fast properties. On agar these species yield a fairly free, often mealy-looking, friable growth, which in the absence of pigment formation, as in the case of *Streptothrix nocardii*, may closely resemble in general appearance a typical culture of *B. tuberculosis*. Growth takes place on potato in most cases; inspissated blood-serum is not liquefied; and the cultures have not any peculiar smell. The pathogenetic action of these species is usually well marked when tested on laboratory animals. Special reference to the acid-fast properties of some of these species will be made later (*vide* p. 319). Lastly, a number of cases have been recorded in which the streptothrix isolated has yielded such scanty growth on artificial media that difficulties in the identification of species have arisen. In most of the cases referred to the growth obtained on nutrient agar has been very scanty and slow, whilst growth in peptone broth has, as a rule, been somewhat more vigorous. Growth on inspissated blood-serum has been usually very scanty, sometimes with "pitting" of the medium. The growth obtained on solid media is whitish in colour and markedly friable, resembling an extremely scanty growth of *B. tuberculosis*, and usually dies out rapidly under the conditions of artificial culture. Pathogenetic action towards rabbits and guinea-pigs is very uncertain; in some cases the streptothrix has produced characteristic nodules and the animal has died, but in perhaps the majority of cases the organism has apparently been non-pathogenetic. It is impossible to

say how many different species possessing this rather indefinite character have been described: I have isolated organisms of this kind from several cases of infection in man, and believe that amongst them it is possible to differentiate at any rate two species—*Streptothrix hominis* I. and II. Foulerton. I would also include in this group the organisms described by, amongst others, Krause, Hayo Bruns, and Norris and Larkin, from infections in man; Dr. Dean has isolated from a submaxillary abscess in a horse an organism in general characters resembling that described.

The Natural Distribution of the Streptotricheæ, and the Sources of Infection for Man.—Saprophytic streptotricheæ are widely distributed in nature, occurring commonly in air, water, and soil. Parasitic species, whether pathogenetic or not, have also a wide range of existence. Some are found living as parasites on higher members of the vegetable kingdom, such as the streptotricheæ which Berestnew has found on grasses. Mazé also has described streptothrix forms which he found amongst the parasitic colonies attached to the roots of leguminosæ, and apparently similar forms have been met with in the course of more recent investigations into the biology of the root-nodules which are specially common amongst vetches.

Coming to the animal kingdom, the lowest form of life which has been found as the host of streptotricheæ is probably the oyster, the writer having isolated a species resembling one of those which have been found in water from the body-juices of an oyster taken direct from a deep laying in an estuary. Terni isolated an organism, *Streptothrix lacertæ*, from some greyish nodules in the liver of Italian lizards, *L. viridis* and *agilis*. Rossi isolated, from abdominal tumours found in two fowls, a species which he termed *Streptothrix alba, varieta tossica*, in order to distinguish it from a somewhat similar species previously described.

Amongst species infecting higher animals there are *Streptothrix bovis communis* and *Streptothrix nocardii*, which have been already referred to as causing disease in cattle, and a well-differentiated species, *Streptothrix capræ*, isolated by Silberschmidt from the lesions of a disease of the goat; and more or less well-authenticated cases of streptotrichial disease have been described in the pig, horse, dog, rabbit, and other mammalia. In man, in addition to the streptotricheæ which have been found as the causes of definite disease, there are species which not infrequently infest the mouth as apparently harmless parasites, although possibly potential causes of disease.

With regard to the common sources of infection for man we have as yet but little exact information. With the exception of *Streptothrix bovis communis* (*Actinomyces bovis* Harz), which has been identified in only a few of the numerous cases of streptothrix infection in man that have now been investigated under modern bacteriological conditions, none of the species infecting lower animals has yet been found to be the cause of disease in man. But certain of the more freely growing organisms of a pronounced "mould" type, isolated from cases of disease in man,

resemble very closely a certain type of these organisms which is represented by such saprophytic species as *Streptothrix alba* Rossi-Doria, isolated from the air, and *Streptothrix leucea* Foulerton, isolated from sewage effluents and from water. One species, *Streptothrix hominis* IV. Foulerton, isolated from a case of nephrectomy for pyonephritis, is probably identical with *Streptothrix melanotica* C. Price Jones, which was found growing on some bacteriological plates as the result of aerial contamination.

A knowledge of the occupation of those affected by streptotrichial disease is of some value as affording a clue to possible sources of infection. I have had the opportunity during the last seven years of examining material from 39 cases of streptothrix infection, which may be classified as follows :—

Infections of the mouth and of the tissues of the neck	21 cases.
Pulmonary streptotrichosis	7 cases.
Renal streptotrichosis (probably primary infection of the lung)	1 case.
Streptotrichial appendicitis	6 cases.
Right iliac abscess (probably secondary to appendicitis in each case)	3 cases.
Streptotrichial conjunctivitis, with sloughing of the cornea	1 case.

Of the 39 patients from whom material was examined, 36 were under treatment in either the wards or out-patient departments of the Middlesex Hospital, whilst 3 occurred in private practice ; of the last, 2 cases are classified in the following table as "unoccupied" females, whilst the third was a student of medicine. Of the 36 hospital patients, most were habitually resident in London, but one or two had been sent up for treatment from rural districts :—

[TABLE

Occupation and Ages in 39 Cases of Streptothrix Infection

Occupation.	Age.								
	All Ages.		Under 15.	15 and under 25.	25 and under 35.	35 and under 45.	45 and under 55.	55 and upwards.	Other Adults, Age not known.
	M.	F.							
Coachman or Stableman	4	...	...	...	1	1	...	1	1
Gardener	2	...	...	...	...	1	1	...	...
Baker	2	...	...	1	...	...	1	...	...
Tailor	1	...	...	...	...	1	...	...	...
Tailoress	...	3	...	...	2	...	1	...	...
Dressmaker	...	2	...	...	2	...	...	...	...
Timber trade	1	...	...	...	...	...	1	...	...
Cellarman	1	...	...	1	...	...	...	...	...
Medical Practitioner	1	...	...	...	1	...	...	...	...
Student of Medicine	...	1	...	...	1	...	...	...	...
Jeweller	1	...	...	1	..	...	...	...	...
Stone-mason	1	...	...	1	...	...	...	...	...
Commercial Traveller	1	...	..	...	1	..	...	...	...
Unoccupied	2	...	...	1	...	...	1	...	
,,	...	3	...	...	...	...	...	..	3
Housewife, of labouring classes	...	2	...	...	1	...	1	...	...
Dairy-maid	...	1	...	1	...	...	...	...	...
Telegraphist	...	1	...	1	...	...	...	...	...
Washerwoman	...	1	...	...	...	1	...	..	...
Schoolgirl	...	2	2	...	...	...	...	...	...
Not known	5	...	...	3	...	...	...	1	1
,,	...	1	...	...	1	...	...	...	...
	22	17	2	10	10	4	6	2	5

The frequency of primary streptotrichial infection of the mouth in cattle, resulting in the formation of small nodules situated immediately under, and sometimes actually invading, the mucous surface of the dorsum of the tongue, has obviously suggested that herbage may be a special habitat of the streptotricheæ and a possible source of infection. Further, the general belief that these infections are especially liable to occur among those whose occupations bring them into frequent contact with dust emanating from dried grasses, or whose rural occupations render them especially exposed to infection from vegetable sources, is to some extent supported by a consideration of the habits and occupations of the 39 individuals included in the above Table. Thus, there were 4 men employed in stables, constantly handling hay and straw, and possibly addicted to the habit, prevalent amongst those employed in stables, of chewing pieces of straw: in case 3 there was an empyema secondary to pulmonary infection; in case 35 there was a pulmonary abscess, with a secondary focus of infection in the cerebrum; in case 18 there was an abscess of the cheek; and in case 28 an abscess of the neck, which presented itself externally behind the ramus of the mandible, and was followed by several small

abscesses in the subcutaneous tissue in the neighbourhood. Two of the patients were gardeners: in case 8 there was an abscess situated in the floor of the mouth; and in case 26 there was a submaxillary abscess presenting itself externally. Two cases occurred in bakers: case 25, in which there was a large right iliac abscess, presumably secondary to appendicitis; and case 27 with an abscess of the mandible. Case 13 was a dairy-maid with an abscess of the cheek.

In addition to these 9 patients who, because of their occupation, may be considered as specially liable to infection from vegetable sources, there were 3 other cases in which there were special reasons to believe that infection might have been similarly conveyed. Case 12 was that of a female student of medicine who died with extensive retro-peritoneal suppuration secondary to appendicitis. Three months before the onset of the first symptoms of appendicitis the patient had spent a holiday in a rural district in Scotland, and had been in the habit of frequently chewing ears of growing barley and oats as she walked through the fields. Case 23 was that of a cellarman with appendicitis; this patient lived over some stables in a mews in London. Case 37, classified as an "unoccupied" male, died with an extensive pulmonary streptotrichosis, a large focus of infection in the liver, and another in the cerebrum. The history of this case was that after an attack of scarlet fever the patient had spent some weeks on a farm in Devonshire; shortly after leaving the farm the first evidence of infection was manifested in an empyema, and death occurred about four months afterwards. To these 12 cases may be added a group of 6 others occurring amongst those occupied in tailoring, or dressmaking, and possibly in the habit of passing cotton or thread between their lips. Case 22 was that of a tailor with an abscess of the mandible: case 1, a tailoress with pulmonary streptotrichosis: case 21, a tailoress with an abscess of the mandible: case 36, a tailoress with an acute parotid abscess: case 24, a dressmaker with a submaxillary abscess which presented externally: and case 33, a dressmaker, died after an operation for streptotrichial appendicitis, with extensive suppurative thrombosis of the superior mesenteric, splenic, and portal veins, which after death were found to be densely infected with a streptothrix.

Amongst the 39 cases, then, there were 18 at least in which there were reasonable probabilities that the infection might have been derived from a vegetable source. The occurrence of two cases amongst bakers is of some interest as suggesting a possible explanation of a portion of the high mortality from phthisis among flour-workers: there is no evidence that this phthisis is due to *B. tuberculosis*, and the association of streptotricheæ with grain suggests the possible nature of some of the cases occurring amongst those engaged in handling flour. In some of the cases of alveolar abscess of the mandible there was evidence that infection had occurred through a carious tooth.

The Pathogenetic Action of the Streptotricheæ.—The most common anatomical manifestation of a streptothrix infection results from the development of nodules and larger masses of granulomatous tissue around the invading parasites. This newly-formed tissue may undergo any, or all, of the changes to which such tissue is liable when developed in the course of an infection by a vegetable parasite: that is to say, the parasite having died out, the newly-formed tissue may disappear, leaving the part

but little altered in appearance and the site of infection marked only by an insignificant cicatrix; or the granuloma may caseate, and sometimes become calcified; or the new tissue may slowly break down into a purulent fluid, or may undergo necrotic changes in mass. Then again, some of the streptotricheæ are actively pyogenetic under certain conditions, and an acute abscess may mark the site of infection.

Speaking generally, it may be said that the streptotricheæ which are the cause of human infections are not by themselves apt to produce any very marked constitutional symptoms or effects, either by the secretion of actively virulent toxins or by the production of like bodies by decomposition of the tissues in which they may be growing. But some of the streptotricheæ have a fairly active local action, evidenced by the formation of acute abscesses and explained in part by the fact that some of them secrete actively peptonising ferments.

The uncomplicated action of the streptotricheæ, then, is not usually manifested by severe general symptoms, but rather shews itself in the physical results of the formation of new tissue, and in the results of destruction of the tissues actually infected. Generally it is only when the granulomatous tissue, having broken down, has become the seat of secondary infection by pyogenetic cocci, or other organisms which secrete toxins that have a marked general effect, that the wasting and more severe constitutional symptoms which occur in advanced cases of streptotrichosis are seen.

The accomplishment of a natural cure in streptotrichoses would seem to be comparatively frequent, and must be borne in mind when considering cases of apparently curative action of drugs. The tendency to natural cure must also be remembered as a possible explanation of cases in which streptotrichial lesions occur only in parts which would not seem liable to become the seat of a primary infection from without; thus, in a single focus of infection in the liver it is always possible that there may have been a primary infection of some part of the intestinal canal, the initial lesion having meanwhile become healed. In fact, there is good reason to believe that the life of individual organisms in the infected tissues is but short, and it is probable that the conditions of parasitic existence in the tissues, unless the lesion is so circumstanced that air has access to the organisms, are not favourable to sporulation. Hence, when the organisms are confined in a limited space, as, for instance, in an abscess-cavity or in an empyema, they probably soon die out; this probability affords an explanation of some of the numerous cases in which it is impossible to obtain any growth on artificial media from material in which an abundance of streptotrichial forms can be seen under the microscope. When there is a progressive invasion of the tissues, however, or when dissemination in remote parts occurs, the parasites grow with renewed life in the fresh soil.

With regard to the spread of infection by direct continuity, or by contiguity, of tissues, there are marked contrasts in the selected path of infection in different circumstances. Thus, at one time a progressive

invasion of fresh tissue occurs without regard to anatomical boundaries, as is not infrequently seen in the course of a pulmonary streptotrichosis. In such a case the parasite from the lung may infect a comparatively small area of the pleural membrane, and, then passing directly through the chest-wall, give rise to an external abscess. This perforating tendency is very marked in some forms of pulmonary streptotrichosis ; and is probably much more common, not merely relatively to the number of diagnosed cases but absolutely, in cases recognised as pulmonary streptotrichosis than in cases recognised as pulmonary tuberculosis. But in other circumstances one observes a marked tendency for the path of infection to run along planes of subcutaneous or other connective tissue : for instance, after perforation of the chest-wall there may be a widely spreading infection of the subcutaneous tissue of the chest, after an appendicitis there may be an extensive infection of the retro-peritoneal cellular tissue, or after an infection of some part of the mouth there may be progressive infection of the subcutaneous tissue of the front of the neck.

Dissemination of the parasite from earlier foci of infection occurs both by the lymphatics and by the blood-vessels. Spread of infection along the lymphatics may be seen in its most typical form in the experimental infection of lower animals by such a species as *Streptothrix nocardii*, when under appropriate conditions the orderly progress of infection by the lymph-paths may be as obvious as in the case of infection by *B. tuberculosis* in similar experimental circumstances. That infection by means of the blood-vessels also occurs is clearly demonstrated by the distribution of the secondary lesions in many cases of human disease.

When invasion of healthy parts occurs, whether through direct continuity of tissue or by dissemination by lymphatics or blood-vessels, it is probable that the organism is usually conveyed in the form of short rod-segments, and not in the smaller spore-form. In some circumstances, as when a suppurating cavity in the lung is in communication with the air, spore-forms may be present in abundance, and being conveyed elsewhere may doubtless originate fresh foci of infection. But in lesions to which air has not had access the organism is found, according to my experience, generally in the typical mycelial form or as shorter rod-segments. And on examining sections of tissues at the edge of a spreading area of infection the earliest forms of the parasite seen are usually such as would suggest that growth of the organism is occurring by the sprouting out of a single rod-segment, or perhaps a collection of two or three, rather than that the parasite is from the first developing in the typical "ray" fashion from a central spore : the ray arrangement of the mycelium in organisms that are growing in the tissues is usually seen only at a comparatively advanced stage, and not in the earliest stage of growth as is observed when development from a spore occurs in a broth culture.

The anatomical distribution of lesions and the clinical course of the disease vary greatly in cases of streptotricheæ in man, and probably

the several species of streptotricheæ which have hitherto been identified have each their special mode of pathogenetic action. But the number of cases in which careful record has been made of both the clinical features of the disease and the bacteriological characters of the infecting parasite is still so small that exact knowledge with regard to this point, such as would be of value in formulating a prognosis, awaits further investigation of individual cases. It is, however, probable that so far as prognosis is concerned, the anatomical situation of the seat of primary infection is as important in streptotrichoses as it is in many bacterial diseases. From this point of view prognosis is generally more and more unfavourable according as infection first occurs in the tissues about the mouth, in the intestinal tract, and in the lungs. And, apart from this, it may be added that parasites belonging to the "acid-fast" group of streptotricheæ are especially likely to be the cause of widely disseminated infection, with correspondingly serious results.

The Identification of Streptotricheæ as they occur in Infected Tissues, in Pus, and in Sputum. — To describe the bacteriological procedure necessary for the isolation and identification of different species of streptotricheæ would be outside the scope of the present article, and it is only necessary now to refer very briefly to the appearance of these parasites generally when occurring in morbid material.

With regard to appropriate staining methods it may be stated that Gram's method stains all the known streptotricheæ well except the degenerated portions of the organism when the stage of segmentation is in progress; and this method is generally the most convenient for purposes of diagnosis. Some species also stain by the Ziehl-Neelsen method commonly used for the demonstration of *B. tuberculosis*.

The general appearance of the parasite as it occurs in the tissues in the "ray-fungus" form is well known; but, as already stated, the earliest stage of growth of the parasite in the tissues may appear as a small collection or clump of short rod-segments, the "ray" arrangement becoming obvious only at a slightly more advanced stage of growth. In sections of tissues affected by streptotrichosis there are occasionally collections of very fine round particles which are much smaller than the spores of a streptothrix; these collections probably represent the remains of masses of mycelium which have died out. In examining sections care must be taken not to mistake the rounded transverse section of a filament for a spore, the latter are not found in ordinary circumstances in sections of infected tissue. Reference must also be made to an appearance of "clubbing" at the end of the mycelial filaments, to which some authorities have attached considerable importance in the differentiation of these organisms. This appearance, however, is very variable; "clubs" may be found in one part and not in another of the same case, and I am not inclined at present to attribute much specific importance to their presence. In pus the adult parasites take the form of dense tufts of mycelium, exactly like those seen in cultures in an artificial fluid medium, and

under these conditions there will never be any difficulty in identifying the nature of the infection. But in the case of an old abscess, in the pus of which the parasite has undergone complete segmentation, there may be great difficulty in differentiating between a streptotrichial and some form of bacillary infection by means of microscopic examination only. Thus in the pus obtained from an old empyema there may only be a number of beaded rods which stain by Gram's method, and at first sight

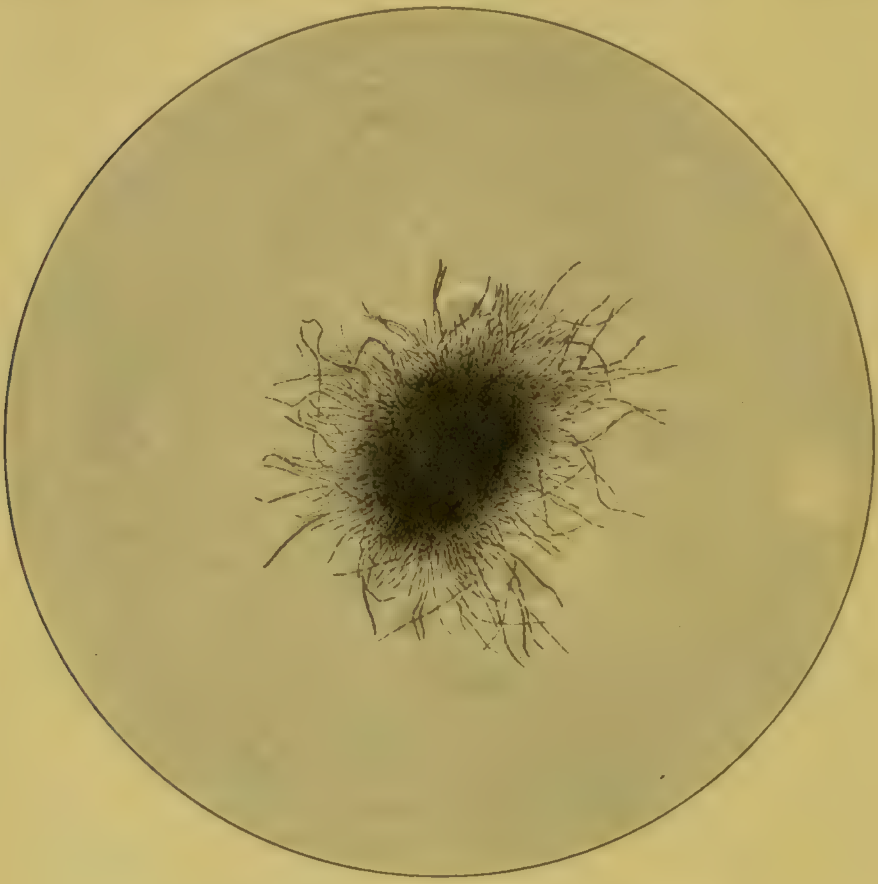

FIG. 4.—Streptothrix parasite in pus from empyema (× about 700).

are not to be distinguished from bacillary forms. But careful examination in such a case will often discover that one or two of the rod-segments have short lateral branches still attached, and possibly some longer filaments with wavy outline will be found. In these cases, of course, cultures will at once settle the question.

In sputum all stages of the organism may frequently be seen side by side, mycelial tufts, small clumps of rod-segments and longer filaments, and sometimes numerous spores, which last, however, cannot be differentiated from ordinary pyococci by microscopic examination. There is,

however, other evidence available as to the nature of these spherical bodies, whose presence, more particularly in the discharge from pulmonary streptotrichoses, is probably due to the fact that the access of air to cavities in the lung favours the sporulation of streptotricheæ that may be growing there. The frequent occurrence of sporulation in the circumstances of pulmonary infection has doubtless some influence in making the prognosis, speaking generally, less favourable in cases of pulmonary streptotrichosis than when the primary lesion of infection is elsewhere.

In some cases the mycelial tufts found in discharges are completely encrusted with gritty crystalline matter which may obscure the nature of the granules until they have been crushed. This crystalline matter retains the anilin stain very deeply when the granules are stained by Gram's method, but its chemical composition is not known. The encrustation of the mycelium is apparently much commoner in bovine than in human streptotrichosis, it is probable that it is peculiar to certain species; further, it may occur not only when the organism is existing under parasitic conditions but also in cultures in ordinary peptone broth. The pus from a streptotrichial abscess in which the parasite is present in pure culture may have a strongly feculent odour; this has been noticed in pus from pulmonary infections as well as in those connected with the vermiform appendix.

The Relationship of Bacillus tuberculosis to the Group of Acid-fast Streptotricheæ.—The question of the existence of a close relationship between the streptotricheæ and certain reputed schizomycetes or fission-fungi—more particularly the parasites which cause glanders, diphtheria, and tuberculosis—has been raised by many pathologists: and evidence of such relationship may be considered in the first place with respect to similarity in general morphology and biological characteristics, and then with respect to similarity of pathogenetic action.

With regard to *Bacillus mallei*, it may be pointed out that the evidence of relationship brought forward is mainly that under certain conditions of culture on artificial media this species assumes "clubbed" filamentous and branching forms (Galli-Vallerio), which certainly resemble some of the rod-segments which may be seen in the culture of a streptothrix after fragmentation of the mycelium has occurred. But it is probable that these morphological variations of the bacillus are merely the accidental "involution" forms of a fission-fungus, and are not comparable with the constantly occurring forms of a regular phase in the normal life-cycle of a streptothrix. For the rest, *B. mallei* is in its method of reproduction a typical fission-fungus, sporulation is not known to occur, and the organism is strongly differentiated from all the known streptotricheæ by not staining with Gram's method. Again, there is no such resemblance between the pathogenetic action of *B. mallei* and the streptotricheæ generally as would of itself suggest any near relationship.

In the case of *Bacillus diphtheriæ* the general morphological similarity of the forms occurring in cultures on artificial media to the rod-segments of many streptotricheæ after the occurrence of fragmentation is, again,

striking; and in both cases good staining is obtained with Gram's method. But neither in cultures growing on artificial media nor by examination of the organism as it has grown in membranes in cases of disease is there any evidence that the bacillus of diphtheria has an early mycelial stage such as is characteristic of the streptotricheæ. Meyerhoff, it is true, has contended that the "clubbed" and branching forms found in cultures of *B. diphtheriæ* under various conditions are the true and characteristic form of the species, but this opinion has not been generally accepted. Nor can it be said that there is any reasonable resemblance between the pathogenetic action of the bacillus and that of the known streptotricheæ; the severe toxæmia, which is the predominating pathological feature of diphtheritic infection, has no counterpart in any cases of streptotrichosis hitherto recorded.

But though for practical purposes these two species must meanwhile continue to be classified amongst the fission-fungi, it is possible that their branched and filamentous forms are not in reality indicative of a degenerative stage in the life of the organism, or are not "involution forms" as they are generally termed, but that they should be regarded as evidence of a commencing evolution of a fission-fungus in the direction of a higher type of life.

With regard to *Bacillus tuberculosis* the position is altogether different, and many, with whom I agree, consider that there are strong reasons for believing that the proper botanical position of this species is amongst the streptotricheæ. The reasons for the transference of *B. tuberculosis* from amongst the fission- to the mould-fungi were first stated at length by Coppen Jones (1895). This writer, after referring to the opinion of Metchnikoff (1888) that *B. tuberculosis* represented not a final stage but only a phase in the life-history of a "thread bacterium," and to the opinion of Fischel (1893) that the species "is no bacillus in the sense of morphology" but in its saprophytic stage when growing on artificial media belongs probably to a family of higher pleomorphic moulds, gave the results of his extensive observations on the morphology of the organism under various conditions, and pointed out the strong resemblance between it and *Actinomyces.* Although very little fresh information has been forthcoming with regard to the biology of *B. tuberculosis*, the considerable additions to our knowledge of the streptotricheæ have strengthened materially the belief held by these writers.

With regard to morphology, it may be said at once that under many conditions of artificial culture *B. tuberculosis* presents forms which are indistinguishable from those assumed by the streptotricheæ, and it is highly probable, but not proved, that the earliest stage of growth of the organism in artificial media is as that of a streptothrix. Further information on this point is necessary; the difficulty which causes the present uncertainty on this point is probably the same as that already mentioned as obscuring the complete morphological cycle of the more slowly-growing streptotricheæ, namely, that segmentation and fragmentation of the mycelium are nearly coincident in point of time. Babes and Levaditi

have shewn that on examining early tuberculous lesions, such as the recent nodules on the dura mater induced by intravenous infection in the rabbit, the "bacillus" is found in a characteristic ray-fungus form; these observations have been confirmed by others.

An important point arising in the consideration of the relationship of *B. tuberculosis* to the fission-fungi on the one hand and to the streptotricheæ on the other is the question of thermic death-point, which itself is intimately connected with the question of spore-formation. And, although this has not hitherto been pointed out, the evidence obtainable in this direction is strongly in favour of relationship with the streptotricheæ. The thermic death-point of *B. tuberculosis* has long been recognised by bacteriologists as anomalous for a bacillus. Thus, with exposure to moist heat for a period of from 10 to 15 minutes the thermic death-point of the bacillaceæ is either between 55° C. and 65° C., or at 100° C., or upwards, according as the organism tested is a sporing or a non-sporing one, while the thermic death-point of *B. tuberculosis* is intermediate in position. The exact thermic death-point of *B. tuberculosis* as a matter of fact has not yet been ascertained, possibly because more than one species is at present recognised under the name, or possibly because of the occurrence of spore-forms in the cultures tested, but the majority of observers place it between 70° C. and 85° C.; I have, however, observed one strain with a thermic death-point as high as 90° C. with an exposure to moist heat of 15 minutes' duration. But, at any rate, these thermic death-points, anomalous for a bacillus whether in a sporing or non-sporing stage, are at once explained by the hypothesis that it is a mould. The thermic death-points of the mould-fungi vary within wide limits; and the observations of Dr. C. Price Jones and myself shewed that for many streptotricheæ examined, the thermic death-points, with a time-exposure of 30 minutes, were between 60° C. and 75° C. Further, with the streptotricheæ, as with other moulds, the difference between the thermic death-points of the same organism, according as it is in an actively growing or in a sporulating stage, is not nearly as great as it is with the bacillaceæ, a range of temperature between 5° and 15° C., representing the difference in species of streptotricheæ selected for the testing of this point.

We may next consider the "acid-fast" property, due to the presence of a waxy substance that enters into chemical combination with the fuchsin used in the Ziehl-Neelsen method, which is common to a group of the streptotricheæ, *B. tuberculosis,* and certain other reputed bacillaceæ. The number of acid-fast streptotricheæ as yet isolated and carefully described is comparatively small; and the more important species have already been mentioned, namely, *S. eppingeri* and the organism described by Sabrazès and Rivière occurring in man, and *S. nocardii* and *S. capræ* occurring in lower animals. I have examined cultures of all these and have found that portions of three of them were identical with *B. tuberculosis* as regards both "acid-fast" and "alcohol-fast" properties. The fourth species, a reputed culture of the organism isolated

by Sabrazès and Rivière, was acid-fast after treatment with a 33 per cent solution of nitric acid, but was decolorised by a subsequent washing with absolute alcohol. In these streptotricheæ the "acid-fast" properties are not present in the earlier stages of growth, and are probably only acquired after segmentation has occurred; further, the number of acid-fast segments in these four species, while increasing as the culture ages, is always limited, so that in cultures up to eight weeks old the acid-fast rod-segments are always present in much smaller number than the rod-segments which have not developed this property. As to how far cultures of *B. tuberculosis* correspond with cultures of these streptotricheæ as regards the acquirement of acid-fast properties we are at present without accurate information, although as long ago as 1889 Dr. Klein pointed out that the bacilli were not acid-fast in the earlier stage of their growth. It must be noted that as regards the four streptotricheæ mentioned it is only the rod-segments that acquire acid-fast properties, the spores not staining either by the Ziehl-Neelsen or by the Moeller method.

Amongst other points bearing on the question at issue are the striking similarity between the appearances of cultures on artificial media of *B. tuberculosis* and of certain of the streptotricheæ, such as *S. nocardii*, and also the comparative difficulty in first transplanting both *B. tuberculosis* and some of the streptotricheæ from parasitic to saprophytic conditions, and the slowness and scantiness of its growth in the first cultures obtained on artificial media. In short, with the exception of the single doubtful point as to whether *B. tuberculosis* in its earliest stage of growth develops from a spore in typical streptothrix fashion, there is no point of essential difference with regard either to morphology or to biology generally that can be raised against the acceptance of the generic relationship of this organism to the group of acid-fast streptotricheæ. While there is so obvious a general resemblance between the mode of pathogenetic action of *B. tuberculosis* and of the streptotricheæ as a class that streptotrichoses have been included amongst the diseases sometimes designated by the ill-chosen term "Pseudo-tuberculosis" (40), it is specially interesting to compare the bacillus in this respect with members of the group of acid-fast streptotricheæ. First with regard to experimental infections, intra-peritoneal injection of a culture of *S. nocardii* or *S. eppingeri* into a guinea-pig gives rise to what can only be described anatomically as a generalised tuberculosis; the results of experimental infection under these conditions with either species are practically indistinguishable, both between themselves and from the results of a similar infection by *B. tuberculosis.* Further, in all the three cases, examination of either "smear" preparations from the nodules of granulomatous tissue or of sections prepared in the ordinary way will shew rod-segments which stain by the Ziehl-Neelsen method—the specific differentiation of the nature of the three infections can, in fact, only be effected by the isolation of the parasite concerned, and the study of its cultural characteristics. With *S. nocardii*, in particular, experimental infection of the subcutaneous tissue is followed by an abscess at the site of inocula-

tion, with a progressive infection of the lymphatics leading from the spot and of the glands into which the lymphatics pass; but according to Nocard the general course of infection is slower in the circumstances than would be the case with *B. tuberculosis.*

Whilst there is this obvious similarity in the pathogenetic action of *B. tuberculosis* and the two acid-fast streptotricheæ under experimental conditions, the number of recorded cases of streptotrichosis in man from which acid-fast organisms have been isolated is still so small that it would be unprofitable to attempt any comparison between them, as apart from cases of streptotrichosis generally, and the different forms of tuberculosis. The following, however, may be mentioned amongst cases of infection due to this particular group of streptotricheæ as illustrative of the lesions which may occur.

Eppinger's patient, a glass-polisher aged fifty-two years, was admitted into hospital with a diagnosis of meningitis. After death the following lesions were found: a "pseudo-tuberculosis" of the lungs and pleuræ, with old caseous nodules in the apices and calcareous degeneration of the bronchial and supra-clavicular glands, together with a cerebral abscess which had ruptured into the ventricles. *S. eppingeri* was isolated from the lesions. Aoyama and Miyamoto isolated what was apparently the same streptothrix from the sputum and from the pus found in cavities in the lung in a case which is described as having been clinically like that of Eppinger's. Major Birt and Col. Leishman have recorded a case in which small nodules were found in the lung, with an empyema and pericarditis. The organism isolated from the lesions was an acid-fast streptothrix which the writers think could be differentiated from Eppinger's streptothrix in certain details of its cultural characteristics, although the general resemblance was marked. In Dr. Stuart M'Donald's case there were miliary nodules, some of which had a caseous appearance, in both lungs, and numerous small abscesses in the kidneys and in the cerebrum. Dr. M'Donald, after a careful comparison of the cultural characteristics of the acid-fast organism isolated from his case and that obtained from Eppinger's case, came to the conclusion that the two were identical. Ferré and Faguet, and MacCallum have also isolated streptotricheæ, which they described as resembling Eppinger's species, although no mention is made of acid-fast properties: Ferré and Faguet's case was one of cerebral abscesses in the centrum ovale, and MacCallum's one of a child with peritonitis, fatal some three weeks after gastrostomy for the relief of a simple stricture of the œsophagus. The streptothrix described by Sabrazès and Rivière was isolated from two cases, in one of which there was a cerebral abscess and a suppurating infarct in one kidney, in the other, bronchopneumonia and multiple small abscesses in the subcutaneous tissue. Scheele and Petruschky have recorded a case of bronchopneumonia with subcutaneous abscesses in various parts of the body. An acid-fast streptothrix was identified microscopically in the sputum, and a streptothrix was isolated from the pus of the subcutaneous abscesses, but no details are given by which the species can be identified.

Flexner has recorded a case of "pseudo-tuberculosis" in a man aged seventy years; "the symptoms were broadly those of pulmonary tuberculosis," and after death gross changes in the lungs, including consolidation, excavation, and caseous and calcified nodules, such as would usually be considered indicative of

the condition diagnosed during life, were found. Microscopical examination, however, shewed the presence of an acid-fast streptothrix in the lesions, but no cultures of the organism could be obtained. The negative result of inoculation of a guinea-pig proved the absence of *B. tuberculosis*.

The close similarity in the pathogenetic action of some of the streptotricheæ and *B. tuberculosis* naturally results in a similarity in the clinical course of the several infections; this is more particularly noticeable in, but not by any means confined to, cases of primary pulmonary disease. In fact it may be said that the anatomical conditions, upon which the production of the physical signs diagnostic of pulmonary disease depends, are identical in many cases of streptotrichosis and tuberculosis, while there are no distinctive symptoms which will assist in differentiation. Under certain conditions the perforative tendency in pulmonary streptotrichosis may afford a valuable clue: thus Sir Richard Douglas-Powell writes, "Closely allied in intimate pathology to tuberculosis, actinomycosis differs strikingly in one important feature of its clinical pathology—viz. its disposition to invasion beyond the bounds of the organ first attacked, *across country*, so to speak, through adjacent tissues to other parts or organs" (cf. p. 335).

The *diagnosis between pulmonary streptotrichosis and tuberculosis* will therefore often, and especially in early cases, depend upon the identification of the causative parasite in the sputum. Should the infecting parasite be a streptothrix not possessed of acid-fast properties, it will probably be readily recognised as such; and the results of the experimental inoculation of animals, if need be, will serve to eliminate the possibility of any tuberculous infection. But, on the other hand, if the infecting streptothrix be one of the acid-fast group, the difficulty of diagnosis between the condition and what is recognised as pulmonary tuberculosis by bacteriological methods may be considerable; in fact it is probable that in a large majority of such cases no such differential diagnosis will be made, in an early stage of the disease at any rate. Microscopic examination of the sputum after staining by the Ziehl-Neelsen method will almost certainly fail to establish the diagnosis between the two conditions. And if recourse is taken to experimental inoculation of guinea-pigs the anatomical lesions in the two cases may be indistinguishable, so that it will be only by isolation of the parasite in pure culture from the lesions of the infected animal that the nature of the infection will be established.

In conclusion, it may be pointed out that should a more exact knowledge of the biology of what is now recognised as *B. tuberculosis* support the contention as to its botanical position amongst the streptotricheæ, there will still remain the difficulty which has arisen in the minds of some with regard to accepting the various phenomena of disease which, as they occur under different conditions in man and lower animals, are recognised under the name of tuberculosis and as being the results in every case of infection by the same species of parasite. Increased biological knowledge of a kind which would enable us to settle definitely

the botanical position of *B. tuberculosis* would, however, also probably decide the question as to the unity of tuberculous infection.

It has not been possible in this article to consider the relationship of various other acid-fast reputed bacillaceæ to *B. tuberculosis* on the one hand and to the streptotricheæ on the other; and for information on this matter, which has an intimate bearing on the question which has been under discussion, the reader may be referred especially to the papers by Moeller and by Abbott and Gildersleeve.

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A. G. R. F.

ACTINOMYCOSIS

(Streptotrichosis)

By T. D. Acland, M.D.

Actinomycosis (ἀκτίς a ray, μύκης a fungus) is the name given, on the authority of the botanist Harz, to a chronic infective disease which occurs in cattle. The parasitic nature of the disease was first[1] fully recognised and its specific characters described by Bollinger (15). The name was derived from the characteristic appearance of a micro-parasite

[1] Although the credit belongs to Bollinger of first securing general attention to the true nature of the parasite, and of shewing it to be the cause of various diseases believed to be dissimilar, many observers had previously recognised it in the tumours of cattle, some such as Hahn (16), Perroncito, and Rivolta (135), had suspected its vegetable origin, and v. Langenbeck (71) had not only detected it, but described it as a fungus more than thirty years previously. See historical summary.

which was found in the affected tissues. J. Israel (71) applied the same name to a morbid condition which he first described as a specific disease in man, without asserting that it was identical with that which had been found in cattle.

Both in man and in cattle the disease presents the same general symptoms, viz. chronic inflammation with the formation of granulomatous tumours, which tend to undergo suppuration, fibrosis, or calcification. It was at first supposed that the parasite was the same in all cases, whether in man or in cattle. Variations in structure were found, but they were attributed to variations in growth rather than to the presence of different species of similar organisms, as has been established by more recent investigations. It is now recognised that the term actinomycosis might equally well be applied to a considerable number of affections caused by similar, but not identical, organisms which belong to the group streptothrix (p. 302). It is probable that the pathological changes which J. Israel first described as actinomycosis in man were not, as generally assumed, caused by identically the same parasite as that which had been investigated by Bollinger in cattle. The relationship of these various organisms which have been found in cases recorded as actinomycosis has been discussed by Mr. Foulerton (p. 302).

History.—Up to the year 1876 the true nature of actinomycosis had, with rare exceptions, been overlooked; cases in cattle were known under a variety of names, such as wens, scrofulous or tubercular tumours, osteo-sarcoma, spina ventosa, and many others; and the positions in which the local affection was more commonly found were indicated by such names as wooden, scirrhous, indurated, or ulcerated tongue; polypus or lymphoma of the throat.

It is probable, however, that actinomycosis is not a new disease in man. As long ago as 1845, v. Langenbeck made drawings of some bodies found in pus from a case of caries of the vertebræ. The notes and drawings were published by Israel (71) more than thirty years later, and there can be no doubt that the case was one of actinomycosis. A parallel to this has occurred in England. In 1896 Dr. Kanthack (80*a*) published some drawings, reproduced from notes made by Sir T. Smith, about the year 1855, on an obscure case of tumour of the upper jaw, which had been under the care of Sir James Paget. The drawings represent an organism closely resembling a ray-fungus; the case probably was one of actinomycosis bovis.[1]

[1] In Plate I. in "the Third Fasciculus of Anatomical Drawings selected from the collection of Morbid Anatomy in the Army Medical Museum at Chatham," London, 1838, a series of drawings is given representing "a species of organic disease of the liver of an obscure kind, and, as it is believed, not yet described." Figures 1, 2, and 3 shew different "portions of the same liver containing numerous well-defined excavations, probably formed by the softening and breaking down of a peculiar tubercular matter." Figures 4, 5, and 6 present more or less similar appearances, but there is nothing in the drawings or in the description to indicate what the true nature of the disease is, and although it is possible that they may have been actinomycosis there is no suggestion made that they were of parasitic origin, nor is there any drawing given of the microscopical appearances of the contents of the scattered foci of disease.

In 1848 (86) Lebert made drawings of some minute spherical bodies which were found in the thick gelatinous pus obtained from a case of thoracic abscess under the care of Louis. The drawings are excellent and unmistakable. The minute bodies, as large as a pin's head, yellow, with a tinge of green, are described as "corps particuliers trouvés dans du pus," without any definite indication of their nature or origin. As the result of a microscopical and chemical examination, Lebert arrived at the conclusion that, being neither albuminous nor fatty bodies, they might be the remains of some parasitic worm, and that the radiating, wedge-shaped bodies might possibly be hooklets, though he was unable to detect any traces of echinococci or cysticerci.

In 1868 Rivolta (135) described some short, rod-like bodies, resembling those of the retina, which he had found in pus from a tumour of the lower jaw of an ox.

In 1871 Robin (137) described and figured some yellowish grains which he had found in two or three cases of chronic abscess; he does not give any clinical history of the cases from which the pus was obtained, but describes the masses as being composed of minute elements swollen at one end, tapering at the other, and radiating from a common centre which consisted of granular matter.

In the following year Heller (59) had under observation a case which he published later as one of "Actinomycosis, running the course of an acute infectious disease"; he made some drawings at the time, which doubtless were taken from colonies of actinomyces.

In 1875 Perroncito described the appearance of the micro-organism in a case of so-called osteo-sarcoma of the jaw, in an ox. He suspected that it might be cryptogamic, and this suspicion was subsequently confirmed by Rivolta (135).

None of these observers, however, proved conclusively the true nature of the cases which they described.

In 1876 Bollinger (15) threw an entirely new light on the subject by the accurate description and identification of a characteristic micro-organism, which has given the name to the disease. His investigations applied only to cattle, but in the following year J. Israel (71) described a similar affection in man, and in 1879 Ponfick (127, 129) brought forward strong evidence to prove the identity of the disease in man with that which had been found in cattle.

It is now generally admitted that there are many forms of actinomycosis, and that some of them are found both in man and in cattle, although no causal relationship has been definitely traced between them. Since the publication of Israel's paper a large number of cases have been reported in almost every part of the known world, and the disease has been found to affect horses, dogs (7), pigs (154, 61), antelopes (13), and elephants (30), as well as man and cattle. Illich (67) in 1892 gave references to 421 cases in man, and Prof. Leith (88) in 1894 gave tabular statements of nearly 450 collected from the same sources, whilst Rührah

(140) in 1899 had collected no less than 628[1] cases, so that the disease cannot now be regarded as rare, whatever it may have been in the past.

The first case of actinomycosis in this country in which the nature of disease was rendered certain by the demonstration of the micro-parasite in the affected tissues was admitted into St. Thomas's Hospital on October 1, 1884 (55). By employing Gram's method of staining I was enabled (1) to shew the thread form of the streptothrix, the significance of which has been so fully admitted by subsequent observers.[2]

Up to this date the streptothrix form had not been fully recognised, since neither Prof. Israel nor Prof. Koch, to whom the specimens were shewn, considered that they were the same organism as that which had been described by Israel. In connexion with Mr. W. K. Treves' case, mentioned below, it is of historical interest that Prof. Koch shewed the writer some sections of a tumour, sent to him for examination as a sarcoma, by Virchow, which contained long thread-like micro-organisms, the nature of which had not been determined. Previous to this, a case had been published as one of actinomycosis by Mr. W. Knight Treves; his surmise was probably correct, and appears to be justified by the photograph of the patient which he published. This view was, however, rejected by Mr. (now Sir) F. Treves, who shewed the specimens at the Pathological Society. Mr. W. Knight Treves considered that the lesions were not scrofulous, nor due to any growth with which he was acquainted. He found minute yellowish masses in the pus, but he informs me that he has no record of the microscopical appearances of these bodies, which he believed to resemble "the ordinary rosette found in cattle."[3] Since this date a considerable number of cases have occurred in this country; and with Dr. Hichens' help I have collected 109 from various sources.

Pathological Anatomy.—The naked-eye appearances of an organ or tissue affected with actinomycosis vary greatly according to the part diseased, the acute or chronic character of the process, and, probably, its greater or less contamination with pyogenetic organisms. In some tissues the appearances differ but little from those of chronic inflammation; in others, such as in the liver or skin, they are often characteristic; in

[1] In 1899 the total of all the tabulated cases reached 1094, but Rührah rejects 400 of them as being probably counted twice.

[2] Compare plates in the *Transactions of the Pathological Society*, London, 1886, with those of Boström (21).

[3] This case was shewn at the Pathological Society (London), in January 1884, by Sir F. Treves, as a case of actinomycosis, although "no fungus had been found in the discharges," and the "*sulphur-coloured bodies of the consistence of cheese*" "*proved on examination to be made up of small masses of necrosed tissue.*" In May of the same year an account was given of the patient's autopsy and of the pathological anatomy of the case. It was then called "a case of *supposed* actinomycosis," though Sir F. Treves finally concluded that it was a case of "alveolar sarcoma." Mr. Watson Cheyne, to whom the specimens were submitted, failed to discover any micro-organism, and inclined to the belief that the lesions were carcinomatous; Mr. Marcus Beck and Mr. R. J. Godlee made a further report on the microscopical appearances of the tumours and classified them as probably "large-celled sarcoma." They did not find "anything resembling the fungus characteristic" of actinomycosis.

others again, notably in the lungs, the lesions have been frequently mistaken for tubercle.

Fig. 5.—Section of liver affected with actinomycosis. From a photograph of specimen No. 1318 in the St. Thomas's Hospital Museum. In the plate the fibrous stroma is brought into greater prominence than was the case in the fresh state, partly because the specimen was preserved in spirit, and partly because the contents have fallen out of many of the spaces into which the mass is divided.

The illustration (Fig. 5), taken from a specimen in the St. Thomas's Hospital Museum,[1] gives a very complete picture of a typical

[1] For permission to take this photograph I am indebted to the kindness of Mr. S. G. Shattock. See also *St. Thomas's Hospital Reports*, 1885, p. 235, and compare Dr. Harley's drawing in *Med.-Chir. Trans.* 1886, p. 156.

case of the disease in the *liver*. This organ, when affected, is the seat of scattered foci of suppuration, many of which may be aggregated into spheroidal masses, with outlying centres of inflammation. The larger masses are composed of an alveolar framework of fibrous tissue, the meshes of which are filled with inflammatory products, and in the centre of these are embedded the characteristic minute yellow grains which are largely composed of the infective micro-organism.

The individual foci of inflammation vary much in size, from that of a pin's head to a minute point, but do not, as a rule, attain to any considerable dimensions. Their fundamental shape is spherical, but by pressure or contraction of surrounding parts they may be distorted to any form. Their walls, which are composed of fibrous tissue, in parts often deeply pigmented, are of varying thickness—the more chronic the inflammatory process, the thicker the walls. When the contents of this fibrous stroma are removed, a spongy mass, having a peculiarly worm-eaten appearance, is left.

In the *lungs* the lesions have a much less characteristic appearance. In some cases there is merely an acute primary bronchitis, with no sign of the reticular formation described in the liver (88). In others the tissue of the lung may be studded with grey nodules the size of a hemp seed, which, to the naked eye, resemble tuberculous nodules (131).[1] On the other hand, parts of the organ may be converted into tough, fibrous material, with an irregular interlobular distribution, enclosing here and there canary coloured pultaceous masses. In a third class of cases there is diffuse bronchopneumonia with some interstitial thickening, and a tendency to the formation of small abscesses and cavities. The general tendency of the disease in the lungs, as in other organs, is to spread in one direction and to disregard those anatomical boundaries which so often prove a barrier to the extension of tuberculous lesions (cf. p. 335). It is comparatively rare for tuberculous processes to pass directly from one lobe of the lung to another, or to perforate the chest-wall by direct spread of the inflammation. But this distinction between actinomycotic and tuberculous lesions is rather one of degree than of absolute dissimilarity, since I have seen several cases of tuberculous pulmonary lesions which have penetrated the chest-wall, and in the absence of the characteristic organism it cannot be relied on with certainty to substantiate the clinical diagnosis of any particular case. If the case be *chronic* a track of cicatrising fibrous tissue is left behind as the inflammation spreads. If the process be *acute*, or if pyogenetic organisms be present, there is a tendency to the formation of abscesses, with little evidence of cicatrisation (22).

Actinomycosis of the *pleura* may give rise to miliary nodules (76), chronic fibrous thickening with adhesions, serous effusion (26), or empyema. The precise pathological changes being determined by the relative acuteness of the affection rather than by changes which are peculiar to this particular organism.

[1] For illustrations of Pulmonary Actinomycosis, see 89, 132, 65, 103.

The lesions in the *skin* (14, 19*a*, 32, 150) are remarkable, and have been fully described by Dr. Pringle. The following description is taken from a case under his care. On the child's back there were livid, fleshy, sarcomatous-looking outgrowths of mottled purplish-red and yellow colour, varying in size from that of a split pea to a prominent bossy mass, rising abruptly to more than $\frac{3}{8}$ inch above the level of the surrounding skin, and measuring 4 inches by 1 inch. To the touch the growths were soft, pulpy, fluctuating, and not tender. The skin over them was thinned, glistening, and semi-transparent. Every growth presented one or more crateriform, ulcerative openings, from which a clear, rather sticky fluid exuded in large quantities. In some of the larger tumours the ulcerative openings coalesced, forming superficial discharging sores, differing entirely from the hard-edged, punched-out, ragged ulcers which result from the breaking down of syphilitic or tuberculous masses.[1]

The naked-eye appearances of lesions in other parts of the body need not be further particularised. Those in the *brain* and spinal cord have been fully described by Prof. Delépine (43), C. H. Martin, Chiari, Howard, and Delore, and those found in the *digestive tract* by Prof. Leith (90), van der Veer, and others (29), while records of numerous cases will be found in the writings of Ponfick, Israel, and Boström; brief summaries of a large number of cases are also given by Illich.

The pus in most cases is characteristic; it varies in consistency but is apt to be viscid, and to contain numerous minute specks. These granules, which consist of the micro-organisms embedded in a layer of pus-cells, are yellow or brownish by reflected, and often greenish by transmitted light. Under a lens, they look like minute raspberries, being more or less spherical, and with a coarsely granular surface. Unless these characteristic masses are present in the pus or tissue the diagnosis of the disease is often impossible, and becomes a matter of surmise rather than of logical deduction.

If teased up in 0·75 per cent salt solution, and examined without staining, these granules may be found to consist of two or more of the following components:—(*a*) inflammatory cells, (*b*) filaments, (*c*) bulbous or club-shaped, highly refracting bodies, (*d*) cocci. Either of the last two may be absent. In man filaments alone have sometimes been found, in cattle the club-shaped bodies most frequently occur; both in man and in cattle (in lesions which have been open to the air) pyogenetic bacteria are as a rule present in varying numbers. The micro-organisms can be recognised under comparatively low magnifying powers (for example, Zeiss, Obj. D. Oc. 2, with a small stop), but it is preferable to use a $\frac{1}{12}$ oil immersion, and to stain the specimens.

Minute Structure.—On section, a mature actinomycotic follicle under a moderately high magnifying power[2] is seen to consist (*a*) of a central

[1] For illustrations of Actinomycosis invading the skin, see 9, 32, 41, 68, 84, 108, 133, 150.

[2] Sections of the affected tissues can best be examined after having been hardened in

core of irregularly distributed filaments, cocci in varying numbers, and in the older growths amorphous degenerative products. External to this core is (*b*) a ring of regularly arranged filaments radiating from a common centre. Surrounding this, again, there is (*c*) another ring more or less complete, consisting of club-shaped bodies through which bundles of radiating filaments from the inner zone are often seen to project. External to the clubs is (*d*) an envelope of inflammatory cells, amongst which there may be giant-cells, in some instances containing portions of the fungus within them. In certain positions, as in the liver, the inflammatory cells are again surrounded by a framework of fibrous tissue, and this it is that gives to some actinomycotic lesions the remarkable honeycombed appearance seen so well in Fig. 5.

The relative proportion of filaments, clubs, and "spores" varies greatly in different cases and in different species of organism present (for further details as to these points see Biological Position, and p. 315 *seq.*, also cf. Adami (4). Thus, in cattle a rosette of clubs is frequently present without threads, and in the young rapidly growing colonies in man, the threads may be found without clubs, but in man both threads and clubs are often present when the growth of the fungus is active. The microscopical appearances of the organism are specified in 47 of the British cases. The thread form is stated to have been found in 34, and clubs in 24; in 11 cases both threads and clubs were present.

Anatomical Distribution.—Actinomycosis may attack any organ or tissue of the body, though, as might be expected, the parts most exposed to contact with the external air are found to be the most vulnerable. Most of those who have collected any considerable number of cases of the disease agree that the *primary* or, at any rate, the *maximum* seat of the disease is found in the head and neck in more than half the recorded cases, and that next in numerical order the digestive tract and abdominal viscera are most frequently attacked. Rühráh (140) gives the following numbers, eliminating certain figures for the sake of accuracy.

Situation of Lesion.	No. of Cases.	Per cent.
Head and neck . . .	359	57
Digestive tract and abdominal viscera	132	21
Thoracic viscera . . .	92	14·5
Skin	16	2·5
Doubtful	33	5
Total . .	632	

absolute alcohol, and embedded in celloidin or in paraffin. The threads and cocci are best stained by Gram's or Leishman's methods, the clubs with orcëine or orange rubin. In lesions which have undergone calcareous or fatty degeneration, the structure of the organism frequently cannot be demonstrated without previous treatment with dilute hydrochloric acid and alcohol. For fuller details see bibliography (19, 23, 44, 153). For the microscopic appearances of actinomyces reference may be made to the following plates, see bibliography (1, 24, 38, 40, 104, 115, 156).

The relative incidence of the disease in the cases collected by Illich (421 cases) and Prof. Leith (88) (393 cases) is practically the same. Duvau (123) gives rather different numbers, which are of interest as shewing that the disease is not very rare in positions or organs which have been supposed to be unusual, *e.g.* the brain, spinal cord, and generative organs. Amongst 257 cases he found the following distribution of the lesions, more than one organ being attacked in some of the cases.

Abdomen (excluding liver)	84
Face and neck	70
Thorax (lungs and pleura)	65
Liver	40
Central nervous system	19
Generative organs	19
Œsophagus	7

In 109 cases recorded in the United Kingdom between the years 1884 and 1906, actinomycotic lesions have been found in one or more organs or tissues of the body with the following relative frequency :—

	Total.
Abdomen.—Liver, 32 ; gall-bladder, 1 ; appendix and neighbourhood, 8 ; rectum, 1 ; kidney, 5 ; bladder, 1 ; prostate, 1 ; testicle, 1 ; ovary, 1 ; spleen, 3 ; abdomen other than above, 14	68
Face, Neck, Tongue, and Neighbouring Parts.—Skin, 4 ; tonsil, 2 ; larynx, 1 ; orbit, 1	50
Chest.—Lung, pleura, and chest-wall	29
Brain and Spinal Cord	5
Acute General	9

In 33 of the above cases two or more organs were affected simultaneously.

The less usual seats of the disease seem to be the heart and mediastinum (144), the extremities (18), the spleen (129), kidneys (101), ear (121), and larynx (3, 107).

Rare instances have been recorded in which the *primary* seat of the disease is believed to have been in such parts as the central nervous system (17, 35, 66), the reproductive system (36, 51, 138),[1] and the orbit,[2] but it is obvious that in some of these cases the organism must have found entrance into the body at some distant point, and that the seat of maximum disease, rather than the point of inoculation, was discovered.

Age and Sex.—Of 405 cases recorded by Prof. Leith, of which the *sex* is known, 295 were males and 110 females, so that it would appear that the disease is far more common in men than in women. In 101 of the British cases in which the sex was given, 65 were males, and 36 females. The *age* at which the disease occurred is given in 84 cases: the youngest

[1] See *System of Gynæcology*, pp. 470 (ovary), 495 (tube), 679 (vulva).

[2] Communicated by Dr. W. B. Ransom, of Nottingham. See also two cases of ocular actinomycosis, *Centralbl. f. Pathologie*, Jan. 15, 1895.

of them was 5 years, and the oldest 65. No less than 59 of the cases occurred between the ages of 10 and 40.

Geographical Distribution.—As the recognition of actinomycosis becomes more general, it seems probable that certain countries and districts are more liable to the disease than others, but it is too early to state the ascertained facts in any but general terms. More cases seem to occur in country districts than in towns; but, as might be supposed, more cases are *recognised* where they are looked for, that is in places where attention has been called to the prevalence of the disease. Thus mycetoma, which is comparatively common in some tropical countries, would seem not to have been recognised in America until 1894 (Adami), though, as occurred in England in the case of actinomycosis of the liver (Shattock),[1] specimens had been preserved unknown in museums and have since been recognised in Chicago and Boston. Observers in Germany, France, Russia, Switzerland, England, and America have all contributed their quota of cases of actinomycosis, but there are at present no accurate data for forming any estimate as to the relative frequency of the disease in these countries severally. An attempt has been made to show the distribution of the disease in the various departments of France by Poncet and Berard (123). They give a map which shows at any rate that it is much more frequently recognised and reported in some parts than in others. Further inquiry is needed to draw any useful deductions from these observations.

Invasion.—The means by which the fungus gains entrance into the tissues has been the subject of much inquiry and many ingenious hypotheses. In some cases it would appear certain that it is conveyed by grain (corn or barley) or some foreign body, which has caused a lesion of the mucous membrane of the digestive (25, 157) or respiratory (107) tract, or skin (11, 19, 20); but no evidence has as yet been brought forward to show that an organism, found outside the body, has been cultivated and successfully inoculated into an animal with the reproduction of actinomycosis. What are supposed to have been clumps of actinomyces have been detected in the crypts of the tonsils (75) and in the hollows of decayed teeth (113), and have been considered a possible source of infection. In one instance Israel (69) found a piece of what he believed to be dentine from a tooth embedded in an actinomycotic focus in the lung. Soltmann records a case in a boy who accidentally swallowed an ear of barley grass, and who subsequently suffered much substernal pain. An abscess formed in the sixth right intercostal space, between the spine and scapula, and the ear of grass was found in the pus, which was evacuated; the pain, however, continued, and after a time the case proved to be one of actinomycosis. Boström (21) demonstrated some remains of a cereal in the lesions found in eleven cases which he examined; other cases are recorded in which the disease has followed a wound with a splinter (105), or has occurred in those pursuing agricultural occupations;

[1] Similar specimens have been found in the Museums of the Royal College of Surgeons, No. 2754 A (Shattock), and of St. Bartholomew's Hospital, No. 2239 C (Kanthack).

and Jensen (73, 98) has recorded an epizootic which occurred in Denmark amongst a herd of cattle fed on barley grown on land reclaimed from the sea. In 17 of the British cases the individual affected had either been in the habit of chewing straw, ears of corn, etc., or had been engaged in agricultural pursuits. In 5 of these cases there is sufficient evidence to show that the lesion was caused by the impaction of a cereal, and in three of them the remains of the cereal was found in situ. In one a grass-seed was taken out of the cheek; in another a spear of Italian wheat was removed from the throat; in a third a grain of wheat was found in the appendix; in two others an oat-grain and a husk of oat were known to have been impacted in the tonsils a few days before suppuration occurred, though the grain itself was not actually found. With regard to invasion by the digestive tract it may be noted that actinomycosis has been found to occur in the udders of cows (85, 91), as well as in the human mamma (106), so that the possibility of infection through milk cannot be disregarded.

The direct transmission of the disease from one individual to another of the same species is rendered probable by a case recorded by von Baracz (8), in which a woman suffered from actinomycosis of the face after being brought into close relations with a man who was similarly affected; but such cases are rare, and no case of direct transmission from animal to animal, nor from animal to man, nor vice versa, has been recorded. Though such transmission has been suspected (9), and three cases are reported as having occurred in one family (15). In a report from the Chief of the Bureau of Animal Industry to the Secretary of Agriculture in the United States, it is stated (141) that twenty-one healthy cattle were kept in close quarters with others suffering from actinomycosis without in any case showing signs of infection. From this it is argued that the disease can be transmitted directly from one individual to another only with considerable difficulty, and on rare occasions, and this has been borne out by the observations of other investigators of large experience, such as Sir J. M'Fadyean (98).

Experimental transmission of the disease from one animal to another, and from man to animals both directly and after artificial cultivation, has been successfully accomplished (156). The first successful experiments by direct inoculation seem to have been carried out by Johne (76) in 1880. Three years later J. Israel (70) succeeded in transmitting the disease from man to a rabbit by direct inoculation. He implanted a piece of granulation-tissue from a patient suffering from a thoracic abscess, due to actinomycosis, directly into the peritoneal cavity of a rabbit. About three months afterwards the peritoneal cavity was found studded with tumours of various sizes. The tumours contained the fungus surrounded by granulation-tissue, and the other elements usually found in the lesions characteristic of the disease. These experiments were repeated and confirmed by Prof. Crookshank (39, 40), Rotter, and others, and the transmissibility of the disease from cattle to cattle by direct inoculation has been demonstrated by the researches of

Johne (75, 77) and Ponfick (130). These latter investigations tend also to shew that cattle are more susceptible to inoculation than either dogs or rabbits.

The earliest successful inoculation experiments with the fungus artificially propagated outside the body were carried out by Wolff and Israel (156). Eighteen rabbits and three guinea-pigs were inoculated by the introduction of a small portion of the culture into the abdominal cavity. Of twenty-two animals used for the research two only did not contract the disease, one a rabbit which had been inoculated with sterile agar as a control experiment, the other a sheep in which the inoculation failed to produce any result. In all the cases in which the experiment was successful the peritoneal tumours were similar to those found in the direct inoculations of Johne and Ponfick mentioned above. The small masses were surrounded by a capsule, and had a pulpy interior; in the larger the capsule was dense, and the interior of the mass was divided by fibrous septa, the interstices of which contained the minute grain-like masses so characteristic of actinomycotic lesions. In many of the specimens examined both the club and thread forms of the fungus were detected, but in some of them the threads were predominant, as is frequently the case in man. That the fungus was alive, and had really been instrumental in producing the disease, was further proved by the observation that actinomyces taken from the tumours was, in four cases out of six, successfully cultivated through many generations on agar; and further, that in one of the animals experimented upon, two metastatic actinomycomas developed in the substance of the liver, the contents of which very closely resembled similar lesions in man (155).

The method by which the disease spreads within the body is in most cases by a gradual invasion of the tissues surrounding the point of inoculation. At the seat of infection minute points of inflammation are found, which extend at their periphery, and unite to form large areas of granulation-tissue. These masses are prone to break down in one direction and heal in another, leaving behind dense cicatricial bands. The process often differs widely from that of simple inflammation. In its progress the disease may disregard anatomical boundaries, and invade one tissue after the other, the direction of spread being determined, not by similarity of tissue, but by contiguity, so that all tissues and organs may be alike invaded. Thus, a focus of disease in the liver may spread to the diaphragm, and, perforating it, lead to the formation of an empyema, or to the invasion of the base of the lung. The soft parts become matted together, and as the disease extends long sinuses are formed which, by the discharge of the characteristic pus, often give the first intimation as to the true nature of the disease.

The lymphatics shew no constant tendency to become affected, and when the glands are enlarged the swelling is, as a rule, due to simple inflammation rather than to invasion by the micro-organism.

Metastases, through the vascular system, occur in a certain number of cases, and in this way large areas may be simultaneously infected, as

in a case recorded by Ponfick, in which the left jugular vein was perforated by a mass of the organism, with the subsequent formation of actinomycotic infarcts in the lungs, spleen, brain, and heart (129).

Dr. Moodie has recorded a case in which the primary seat of the disease was in the right upper jaw; metastases occurred in the liver, and from thence invaded the diaphragm and right kidney. Chiari had a case in which metastatic abscesses were formed in the spinal cord, the main lesion being pulmonary in the form of bronchiectasis.

Cultivation.—The organism has been successfully cultivated outside the body by many observers. Boström,[1] in his classical paper, gives the results of several hundred cultures which he made from human and bovine actinomyces. He was successful both under aerobic and anaerobic conditions at 37° C., using gelatin, bouillon, and agar. He did not, however, succeed in reproducing the disease in animals.

In this country Prof. Crookshank carried out a large series of cultures which show that the organism grows readily under suitable conditions, the separate growths spreading peripherally, and forming by their amalgamation larger areas with crescentic or circular outlines like intersecting fairy rings. After a few weeks the growth becomes covered with a whitish or yellowish powdery efflorescence, which under the microscope is found to be composed almost entirely of spore-like bodies. When cultivated on agar the young colonies of actinomyces shew under the microscope a tangle of branching threads, some straight, some twisted, and some with bulbous extremities. As a rule no true clubs, such as are found in animal tissues, develop in cultures, although expansions of the threads having a somewhat similar appearance have been found by Boström in cultures grown under anaerobic conditions. He attributed this to the exhaustion of the nutritive material in the culture medium, and considered it as evidence that the clubs are involution forms.

Biological Position.—Actinomyces was originally believed to be a mould, of which the clubs were the asci or gonidia, and the threads mycelium. The researches of Boström, Wolff and Israel led them to the conclusion that the clubs were involution forms, and that the method of reproduction was by the formation of spores in the filaments, or by their transverse fission.

For all these questions, including the comparative biology and pathology of actinomycosis, and its relations to madura foot and other similar affections, see p. 302; also (152) (106).

Clinical Features

The *incubation-period* is mainly determined by the seat of the primary infection. It varies within very wide limits, it may be as short as a few days if the lesion is in the mouth (52), or as long as two years (105) if the seat of infection is in the extremities.

[1] For coloured drawings of cultures of actinomyces, see References Nos. 53, 26, 115.

The *clinical course* of actinomycosis is generally chronic, but in exceptional cases there is rapid dissemination, owing to the fungus having found entrance into the vascular system with the formation of metastases (45, 66, 101); it then pursues the course of an acute infectious disease (59, 80), or even of pyæmia. Such acute cases are rare, and any considerable pyrexia, suppuration, or septic infection is as a rule caused by accidentally associated pyogenetic organisms.

The manifestations of the disease may be as protean as the organs which the disease attacks are various. When one of the deeply seated viscera alone is involved, there is generally no guide to the real nature of the affection. It is for this reason that so many of the recorded cases have only been recognised after death; during life they have been regarded as abscesses, empyema, appendicitis, abscesses of the liver, vertebral caries, tuberculosis, sarcoma, or even carcinoma. In a large proportion of cases no certain diagnosis can be made until the fungus has been detected under the microscope.

When the skin is invaded the appearance of raised, pulpy, fleshy masses, with minute fistulous openings discharging a thick gelatinous pus, may be characteristic, and certainly should excite suspicion as to the nature of the lesion (32, 133). The presence of the grains in pus may be readily demonstrated by shaking it up in a test-tube with a little salt and water; they will then be seen clinging to the sides of the tube. Their presence renders the diagnosis almost certain so far as the general nature of the affection is concerned, but the more precise differentiation of the species of fungus must be decided by further microscopical examination, since somewhat similar appearances are occasionally seen in pus from tuberculous lesions. As a rule the pus is without odour, and often has a greenish or yellowish tinge, but in actinomycosis of the lungs the sputum may be offensive, the case resembling one of bronchiectasis. If the sputum is sweet, and there is hæmorrhage, the physical signs and symptoms may be precisely similar to those of tuberculosis, or even pneumonia.

From what has been said above, it is evident that actinomycosis of the internal viscera, in which there is no lesion of the skin or discharge of pus, is in *chronic* cases clinically indistinguishable from many other diseases, and the diagnosis in the majority of cases can only be made by the detection of the characteristic micro-parasite in the discharges or evacuations. Any deduction made from the course of the disease, or from the situation and physical signs of the lesions, is liable to be erroneous. In *acute* cases the difficulties are equally insurmountable without the detection of the micro-organism, and a diagnosis which turns out to be correct cannot be regarded as anything more than a fortunate surmise.

Prognosis.—When uncomplicated and local, the disease is dangerous, mainly from the mechanical interference which the neoplasms may exert on organs essential to life. Suppuration and metastases, with their consequences, are the dangers which should excite most apprehension. Just

as in tubercle, the affected tissues may become cicatrised or calcified, and the disease may in this manner be cured, yet in a large proportion of cases in which the viscera are affected, it is steadily progressive, and ends fatally from exhaustion.

In attempting to forecast the probable course of a disease like actinomycosis, it is necessary to take into account such factors as the part or organ affected, whether the lesion is superficial or deep, whether it is complicated by suppuration, or whether the spread has been by contact or metastasis. Thus, it will be found that whereas actinomycosis of the skin is rarely fatal and is readily amenable to treatment, disease of the internal viscera is generally fatal, since no case of recovery after actinomycosis of the liver or brain has so far been recorded. Dr. Hichens has put on record a case of pulmonary actinomycosis which at the time of writing had apparently made a complete recovery, but such a result cannot be expected with any confidence.

The mortality in the various forms of the disease in 257 cases collected by Duvau, and quoted by Poncet and Berard (123), was as follows :—

Position of Lesion.	Deaths per cent.
Skin	2·3
Face and neck (superficial lesions) . .	10
Jaw and temporal region (deep lesions) .	30
Intestinal and abdominal cavity . .	65
Intra-thoracic (pulmonary and pleural) .	85
Liver.	100
Brain and spinal cord	100

The visceral lesions are so fatal, partly because as a rule they are secondary to some other local infection, and partly owing to the fact that they cannot be satisfactorily reached by surgical means. The spread of the organism is usually slow, and in cases in which the lesion is superficial and within reach of local treatment, provided that there be little suppuration and no metastases, a favourable prognosis may be given.

Treatment.—Two methods of treatment have been found specially useful : the internal administration of iodide of potassium in large doses, and the total excision of the part affected. Improvement under the use of eucalyptus oil has also been recorded (64, 140). Other means, such as X-rays (57), injections of tuberculin (12), "bacterien protein" (160), injections of iodine, and decomposition with the electric current (42) have been tried and found to be of temporary benefit (58). Von Baracz (9) has suggested the use of intravenous injection of silver preparations, but does not give details of any cases in which this method had been actually tried. Many years ago Thomassen first used iodide of potassium, and the local application of iodine to the diseased tissues in

cattle. In 1891-92 a series of cases was similarly treated at Chicago (141), of which 63 are said to have recovered, and Nocard (111), Sir J. M'Fadyean (99), Buzzi, and Dr. Ransom (134) have recorded cases in man in which the same drug had been used with marked success. Since it was first tried many cases have been treated with the iodides, and with such apparent benefit that its use is indicated in increasing doses when once the diagnosis has been made with certainty. In man the dose should reach at least 45-60 grs. per diem; in cattle as much as 240 grs. has been given. As an alternative to the excision of the affected parts when they are accessible, scraping, combined with the local application of nitrate of silver, corrosive sublimate in solution, iodoform, or some other antiseptic, may be of service. The organism is fortunately susceptible to such methods of treatment; its vitality is low, and if the diseased part can be reached with safety, the affection in a large proportion of cases can be permanently cured.

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CONSTITUTIONAL SYPHILIS

By JONATHAN HUTCHINSON, F.R.S.

THE specific fever known as Syphilis differs chiefly from its congeners in the much more prolonged duration of its several stages. Like small-pox, measles, scarlet fever, and the others in this group, it is communicable from the diseased to the healthy, and can be produced by no other means. Like them it has its several stages of incubation, efflorescence, relapses, decline, and sequels. As in them, so in syphilis, the most prominent symptom is an exanthem or cutaneous rash. The various stages of syphilis tend to pass away of themselves, in the course of time, almost as certainly as do those of small-pox; and one attack affords for a time immunity from a second. As is the case in the other zymotic diseases, the poison of syphilis is one which possesses the power of breeding in the patient's body; and the smallest possible quantity of virus suffices in due time to infect all the solids and fluids of the system. The time required, however, is in it much longer, and the stages are much more protracted. Instead of counting the duration of its stages by days, we have to count by weeks, or by months. From this circumstance there follow, in the most natural manner, certain apparent differences between syphilis and the other fevers. Thus, because the evolution of the exanthem is slow and gradual, the pyrexial disturbance attending it rarely rises to any great height; and because each stage is so much longer, correspondingly wider margins for occasional variation in length must be allowed. It further follows that as the disease extends over years, and its subjects may not be incapacitated by it for social life, many, whilst still infected, become parents, and transmit their taint to their offspring; a circumstance which can but very rarely happen in the more short-lived and acute fevers.[1] These apparent differences are by no means real ones. It is probably by no means correct to allege that syphilis is the only fever which has a tertiary stage. What are called the tertiary symptoms of

[1] Hereditary transmission occurs in all specific fevers if it chance that offspring is produced whilst the parent is suffering.

syphilis find their analogues in many cases of small-pox and scarlet fever, in what are known as the sequels of those diseases; it is true that these occur only in a small proportion of cases, but the same holds good of the tertiary syphilitic phenomena. If we observed more carefully, it is probable that the sequels of the exanthems might be recognised much more often than they now are; and that many of the diseases classed as "strumous"—inflammations of the eye, the ear, or the skin, or again some diseases of bones and joints—are, at any rate in part, the tertiary consequences of some specific fever. So, too, if it be alleged that the stages of syphilis may be shortened and otherwise modified by treatment, whilst those of the other exanthems cannot, we may reply that those of the latter are too short and transitory to give time for a fair trial of remedies; and further, that it is by no means proved that mercury given with sufficient vigour and promptitude would have no influence over such a disease as small-pox. Syphilis does, fortunately, differ from most of the other specific fevers, in that its virus is incapable of diffusion in the atmosphere, and that consequently it is contagious only, and not infectious also; but it is by no means solitary in this feature.

Etiology.—One of the most noteworthy discoveries of recent times is that of the specific parasite of syphilis. Schaudinn's *Spirochæta pallida* is a very slender spiral filament with serrated borders. It possesses, when free, a rapid undulatory movement, but is sometimes found in masses as if agglutinated. It is stained with difficulty. This organism has now been identified by very numerous observers, and in many different parts of the world, and there can be no doubt that it is frequently present in large numbers in the lesions of primary and secondary syphilis. It has been transferred to apes, which have later shewn the symptoms of syphilis. It has also been identified in the lesions of "Parangi" in Ceylon, a malady which has for long been with good reason claimed as syphilis. Thus far it has not been indisputably discovered in any disease not of a syphilitic nature; we may, therefore, with some confidence assume that the true causal parasite of syphilis has been discovered. Its discovery has in the main been discounted by the general assumption that such a parasite must exist. This assumption was made when syphilis was first claimed as one of the specific fevers, and upon it modern classifications of the stages and various phenomena of the malady have had their basis. It is scarcely to be expected that Schaudinn's invaluable demonstration will do much to advance what careful clinical observation has already affirmed. It is, however, probable that it may lead to new methods of diagnosis and perhaps of treatment, and it is certain that it will add exactitude to research. [For description of the parasite see article on "Protozoa" in volume on "Tropical Diseases and Animal Parasites."]

Having thus defined the rank which true syphilis ought to occupy in our nosological classifications,—a point of the utmost importance to our correct appreciation of its nature,—we may next ask the question, whether under this name we have to deal with one disease or with several. Every surgeon is aware that there are many venereal sores

which are not followed by syphilis, and very different opinions have been entertained of the relation which these hold to the real disease. Some have assumed that there are several distinct poisons; others hold that there are certainly two. Without entering at length into the controversy, it may be remarked that the evidence in favour either of *plurality or of duality*[1] has always been quite inconclusive. Let us accept clearly the doctrine that all forms of inflammation are attended by elements which may prove contagious, and capable of producing disorders similar to those in which they have originated, and we shall not have much difficulty in explaining the different forms of non-syphilitic venereal sores. The majority of the latter are probably *abortive inoculations.* In the performance of vaccination the utmost care is taken to secure the true virus, yet not infrequently abortive sores are produced. If it were the practice to inoculate again from these abortive sores when suppurating, we might soon produce an analogous state of things to what we now have in respect to the soft and hard chancre. The communication of syphilis in social life is, of course, a matter of mere chance, and the virus with which it is effected can be but very seldom in a state of purity. It is probable that very often the secretion which effects it does not contain the specific virus of syphilis in a form capable of its own reproduction. In other instances sores may result from inoculations of a mixed secretion containing the true virus, but with it an irritant capable of producing inflammatory action of a kind likely to be destructive to its vitality. A chancre which ulcerates quickly may very possibly thus rid itself of a virus which would otherwise have gone through its stage of incubation. Further, we must remember that this stage of the primary sore is transitory, and that those who have once had it but seldom have it again. A large proportion of the women by whom contagion is communicated have had syphilis long before, and are incapable of originating the true virus. The sores which they present are analogous to those caused by vaccination in protected persons. These considerations would, I feel confident, enable us to put aside the unnecessary hypothesis of duality.[2]

In an article on the medical aspects of syphilis any detailed consideration of the **primary symptoms** would be out of place. It may be sufficient to say that the success of a syphilitic inoculation is denoted by the formation of a base of induration beneath the abrasion first noticed;

[1] Surely it is absurd to speak of the "duality" of things which have scarcely any features in common. The production of constitutional phenomena is the essential feature of syphilis, and as thus denoted there are not two forms of syphilis. We may freely admit that, in impure sexual intercourse, fluids of very various qualities and endowments may be inoculated, and thus very different kinds of local ulcers may result, but there is only one poison which can produce syphilis.

[2] It is a plausible conjecture that in the non-infecting chancre which never indurates the specific parasite is not present but only its products. The recent discovery of the spirochæta may be expected to afford important elucidation of this point. That the non-infecting "soft" sore is in some way connected with true syphilis, no one can doubt. Those who do not consider the evidence as regards Ducrey's bacillus conclusive may regard it as possible that the *Spirochæta refringens* is the cause of the non-infecting or soft sore. The sores spoken of as chancroids are, however, very variable in character, and may not all be due to the same parasite.

that this induration is seldom well characterised until three weeks or a month after the contagion; that it is usually attended by very little either of ulceration or suppuration, and that it causes an enlargement of the proximal lymphatic glands. The bubo shews the same tendencies as does the chancre. There is hardness, with but little swelling, and rarely much tendency to the formation of pus. These characters will usually be the same, or nearly the same, in both sexes, at all ages, and on all parts of the body. It must, however, be freely admitted that many chancres which infect are yet never indurated. Some writers hold that certain parts never exhibit, when inoculated, the phenomenon of induration. Chancres with well-characterised induration may, however, be met with in most various positions; for example, in the glans penis, the nipple, the lips, the eyelids, the hands, and so on.

Secondary Symptoms.—A successful inoculation having been effected, a *period of incubation* ensues which may last from one to three months, and usually averages about eight weeks. During the latter part of this period the patient is often sensible of some malaise and discomfort, and may be feverish in the evening. At length an exanthem makes its appearance, affecting both the skin and the mucous membranes. The skin shows a scattered eruption, which may vary very considerably in some of its characters, but usually conforms to rule in being of a coppery hue, and in preferring the fronts of the limbs to their dorsal aspects. This rash may be merely congestive, resembling that of measles; or it may be scaly, papular, eczematous, pustular, frambœsial, or bullous. In some few cases it is attended by ulceration, but as a rule it invades only the superficial layers of the skin, differing in this respect from the tertiary manifestations. There is not the slightest reason for believing that these differences in the character of the exanthem imply difference in the nature of the virus. Chancres exactly corresponding in their characters may be followed by most diverse kinds of eruption. Simultaneously with the eruption on the skin we usually observe evidences of similar implication of the mucous surfaces. On the tonsils symmetrical ulcers form; these ulcers are often of kidney-shape, and have a grey base with abrupt edges. They are attended by but little pain, and do not spread much either laterally or in depth. They are often attended by a silvery white discoloration of the adjacent mucous membrane, which may suggest a comparison with the tracks left by snails. After lasting for a few weeks they usually heal. These tonsillar ulcers are rarely absent through the whole of the exanthematous stage, but they may often require careful search. Very often, but not nearly so constantly, we observe also certain superficial patches of inflamed mucous membrane in the mouth, on the pharynx, palate, tongue, or cheeks. On the tongue, at the corners of the mouth, and sometimes in other positions also, these patches become very considerably raised, and assume the condition known as condyloma. If condylomas be observed in the pharynx, they will almost always be found in the anus also, and conversely. They are to be regarded as patches of cutaneous eruption modified by their position and by the

moisture of the parts. Whether or not in these cases any eruption extends through the alimentary canal is a point upon which we have no evidence. That there is in this stage a tendency to overgrowth as well as to inflammatory changes is proved by the occasional production of well-characterised papillomas, especially on the tongue.[1]

The exanthem usually takes from a fortnight to a month before it is fully out, and about two months are usually occupied in its gradual decline. In some cases it is very transitory; in some it is greatly prolonged. When it is at its height, or just when it begins to decline, there occurs, in exceptional cases, an inflammation of the eye. The iritis, when it happens, is usually symmetrical. It is attended by the free effusion of lymph, often in elevated nodules of a salmon or rust tint; the characteristic zone of ciliary congestion is usually well marked, and there is often a dotted deposit in the posterior lamina of the cornea. In other cases, instead of iritis or coincident with it, inflammation of the retina occurs. The retinitis is usually a little later than the iritis, and we rarely see it until the eruption on the skin is disappearing. This form of retinitis is not very uncommon, and is a very insidious and most important malady. The patient notices nothing, excepting that his sight is very dim; he has no pain, no congestion of the front of the eye, no intolerance of light. The ophthalmoscope shews us the retina hazy, and as if stained with port wine; the optic disc slightly swollen and its margins indistinct; and occasionally numerous small extravasations of blood are seen. Very frequently, in association both with iritis and retinitis, the vitreous body is also affected, and a cloud of opacities result. These may lead to difficulty in the recognition of the precise state of the retinæ.

It is currently supposed that syphilitic iritis may occur at almost any period in the course of the disease. I speak after close attention to this subject, when I assert that all our well-marked examples of this disease present themselves amongst the secondary phenomena. From three to six months after the chancre is their usual date. When once iritis has occurred, and adhesions have been left, relapses are liable to happen; and this has led to the error which I am endeavouring to confute. In these relapsing cases, however, the symptoms are very different from those of the first attack. The effusion of lymph is much less free, no nodules are seen, and rarely are both eyes simultaneously affected. There is almost always either rheumatism or true gout.

Whilst the local phenomena just mentioned are occurring, there are usually present others of a less definite character. The patient loses flesh, he is restless and slightly feverish, the appetite is deficient, the bones and joints ache, and the hair becomes dry and thin. Now and then swellings occur on certain bones, more especially on those of the skull; but in this stage periostitis is always slight and transitory, and never suppurates.

[1] See a figure of papillomatous growths on the dorsum of the tongue not condylomatous, in *Illustrations of Clinical Surgery*, Plate LVII. Fig. 2. The demonstration of the occurrence of these hypertrophies of papillæ, as well as the modifications in the condyloma, is of much importance in connexion with "framboesial syphilis."

At this stage also the patient may suddenly become deaf in one or both ears, and now and then facial paralysis attends the deafness.

Such are the various symptoms which mark what is called the secondary stage of syphilis when not treated by mercury. In many cases only a few of them occur, the rash on the skin and the ulcers in the tonsils being the most constant. In many individuals all the secondary symptoms have disappeared within six months of the original contagion; but in a larger number a year elapses before such is the case. It is rare for any symptoms belonging to the secondary group to linger after eighteen months have passed, although their effects are often seen much later. That these symptoms may disappear in a most satisfactory manner, quite irrespective of any efficient treatment, is confirmed by every day's experience. The statements just made are supposed to apply to cases in which mercury has been avoided.

Recurring Eruptions.—Although it is true, as just stated, that the secondary stage is never repeated unless a fresh inoculation has occurred, it must be admitted that in rare instances generalised eruptions do occur at long intervals subsequent to apparent cure, which it is exceedingly difficult to distinguish from those of the secondary stage. Such cases have been recorded both by M. Fournier and myself. Sometimes more than one such attack, with intervals of several years, may occur in the same individual. The eruption is usually a quite superficial one, closely resembling that known as pityriasis rosea, and disappears very quickly and completely when mercury is given. It is never attended by fever or sore throat, and its subjects are sometimes married men whose recently born children shew no signs of taint, and whose wives remain unaffected. All the recorded observations have been made in cases in which prolonged mercurial treatment had been used.

Syphilis Maligna.—The term "malignant syphilis" is applied to certain cases which run a rapid and severe course, and do not easily yield to specifics. It used to be thought that the tertiary stage followed precipitately on the secondary, but this is not exactly the truth. Ulcerating lesions and great failure of health do undoubtedly characterise the cases called malignant, but they are not strictly tertiary. It is the tendency to ulcerate and not the production of gummas which forms the paramount feature in these cases. In some instances this malignant severity is the result simply of neglect of early treatment, and in these the judicious use of specifics is usually promptly effectual. Others and more serious cases are those in which mercury has been used too freely for a while, and under necessity abandoned, but these, too, are hopeful. The worst, and fortunately the rarest, are those in which the patient shows idiosyncrasy as regards mercury. In some of these even very small doses cause ptyalism and inflammation of the throat and mouth, and treatment becomes extremely difficult. It avails little to change the mode of administration, and the only plan is to send the patient to the sea, and to combine quinine with the mercury, carefully adjusting the dose of the latter from week to week. In almost all cases of malignant

syphilis mercury is still the remedy, and in many it must be used boldly.

Tertiary Symptoms.—When the group of secondary symptoms has passed away there usually follows a period of apparent health, during which the patient may believe himself wholly cured. The interval between the well characterised secondary and the well characterised tertiary symptoms is one of different degrees of immunity in different cases. In many persons, probably in a large majority, the disease becomes wholly latent, and the patient experiences nothing whatever to remind him of his taint. In many others, however, recurrences of symptoms, which it is difficult to assign to either group, continue to shew themselves. Superficial sores on the tongue or the mucous membrane of the mouth, isolated patches of scaly or desquamating eruption on the skin, especially psoriasis palmaris, are the most frequent of these. Sometimes they are symmetrical; at other times not so. Such symptoms may continue to recur for many years after the contagion. They probably depend rather on permanent tissue-contamination than on still existing blood-disease. At any rate it may be safely asserted that we never witness any true recurrence of the secondary epoch. The eruption is rarely very copious, and is rarely of such a character as to deceive an experienced eye; nor is it attended by the ulcers on the tonsils, or iritis, which are so common in the secondary stage. In rare instances, at an interval of perhaps a year or eighteen months after infection, a relapse of a general symmetrical rash may occur. This rash may assume the form of rupia, and be attended by severe constitutional symptoms.

Gummas.—Speaking generally, however, after an interval, which may vary in length from a few months to a few years after the cessation of secondary phenomena, symptoms of a different kind may ensue. Inflammatory indurations of a chronic character, and tending slowly to softening and ulceration, occur in the deep-seated tissues, or in the deeper parts of the superficial ones. In this way the skin, the subcutaneous tissue, the periosteum, the muscles, the internal viscera, the organs of special sense, and even the cerebrospinal system itself, may be attacked. A remarkable difference is to be observed between secondary and tertiary symptoms as regards the symmetry of the inflammations produced. In the secondary stage a most definite tendency to symmetry, often very exact, is observed, proving that the producing cause is free in the blood, and is supplied impartially to both halves of the body. In the tertiary stage the lesions are often single, or, if multiple, they display but little accuracy of symmetrical arrangement. This implies that they result from disturbed organisation of the solids, rather than from any poison still existing in the circulating fluids. The occurrence of the tertiary symptoms is to be explained by the fact, that during the exanthematous stage, when the whole blood was loaded with the virus, the various solids received the elements necessary for their growth from poisoned blood. Hence an impairment of organisation in such tissues, and a liability under slight exciting causes, or even in the ordinary course of nutritional

change, to the occurrence of specific forms of inflammation. It is easy to see that in syphilis, with its very prolonged period of blood-poisoning, the risk of permanent tissue-modification must be much greater than in the other fevers. During the exanthem stage of small-pox probably but little in the way of nutrition is effected; the changes being chiefly those of waste and disintegration. From this, it almost necessarily follows that the more prolonged and severe the secondary stage, the greater the risk of tertiary symptoms.

The following is a statement, in tabular form, of the various symptoms of the different stages of syphilis:—

1st Stage.—*Inoculation* and *Incubation*. Average duration, six weeks to two months.	An ulcer with indurated base and but very scanty secretion. Induration of the nearest lymphatic glands, with but little adjacent inflammation or tendency to suppurate.
2nd Stage.—*The Humoral* or *Exanthem* stage, that of secondary symptoms. Average duration, two to six months; may extend over a year, or even much longer. Lesions general, symmetrical, and not serpiginous.	Symmetrical ulcers on the tonsils, not spreading either in width or depth. A symmetrical eruption on the skin. Condylomatous patches on the mucous surfaces, and on the skin adjacent to the mucous orifices, usually symmetrical. Iritis, retinitis, or otitis; mostly symmetrical. Pains in bones and joints. Febrile disturbance. Loss of hair. Slight enlargement of lymphatic glands in all parts. Arteritis and other affections of the blood-vessels.
3rd Stage.—*Interval of latency or of relapses.* May vary from a few months to many years. Symptoms usually persistently local.	In most cases the patient is wholly free from symptoms, but in a certain number reminders occur from time to time in the form of scattered scaly patches or rings, especially on scrotum, psoriasis palmaris, sores on the tongue, lips, etc. Recurring herpes on genitals, or in mouth.
4th Stage.—*Tertiary symptoms or sequels. The stage of gummas.* Of uncertain duration, and often characterised by a remarkable tendency to relapse. Lesions local, not symmetrical, and frequently serpiginous.	Asymmetrical ulcerations in the mouth and throat, tending to spread widely and deeply. Asymmetrical lupoid ulcerations of the skin. Nodes of periosteum, cellular tissue, muscle, tendon, fascia, or nerve; not usually symmetrical, chronic in progress, tending to ulcerate or even to slough. Diseases of viscera, blood-vessels, and nervous system.

Having thus sketched the normal course of syphilis in its several stages and its sequels, we must next consider the conditions under which its orderly evolution may be interfered with. These conditions are, with one very important addition, the effects of specific treatment, precisely the same as those which may disturb the course of any other exanthem. We have, 1st, idiosyncrasy; 2nd, the coexistence of some

diathesis or of some other specific disease; 3rd, immunity, partial or complete, obtained by a previous attack of the same disease; 4th, inherited immunity, partial or complete; 5th, imperfect inoculation; 6th, the influence of treatment.

1st, As regards *idiosyncrasy*, I may simply remark that it is a matter of general experience that certain constitutions resist the specific animal poisons in a most remarkable manner; and, on the other hand, we meet with those who succumb easily and suffer severely. We are unable to offer any explanation of this. The influence of these inexplicable peculiarities in individuals is frequently observed in reference to syphilis.

2nd, The existence of some *special diathesis* or of some *other specific fever* at the time of syphilitic inoculation may modify the course of the latter. Possibly we overrate rather than otherwise the effects of these influences. Although it is not infrequent to find a delicate scrofulous subject suffering with unusual severity from syphilitic poisoning, yet the converse is almost equally common; we often see the delicate escape easily and the robust suffer very severely. There can be little doubt, however, that the tendency to suppuration and ulceration is much greater in those of fair skin and sanguine temperament than it is in others. The influence of diathesis (scrofula) also often makes itself felt in preventing recourse to specific treatment. There is probably no reason to believe that the existence either of a special diathesis or of another specific fever will materially modify the duration of the several stages of syphilis.

3rd, *A previous attack of the same disease* is well known to exert a most important influence upon the course of a second in the same individual. It is generally understood that syphilis, once had, is protective in the majority of cases against any second attack; and second attacks when they do occur are much modified. There is reason to believe that second inoculations are common, and that they usually end in the production only of the soft chancre (abortive sore). It is, however, quite certain that second infections of syphilis may be followed by the full phenomena of the disease.

4th, Of yet wider importance is the question of *the influence of disease in the parent in affording protection, partial or complete, to the offspring.* If we grant, as we must, the two postulates—first, that syphilis is transmissible to offspring; and, secondly, that it is protective for a certain time against second contagion—then we are obliged to admit that just as the disease itself may be transmitted, so may the immunity which it affords. Here again it is very difficult to obtain trustworthy clinical evidence on which to build. There can be little doubt that those who have suffered in infancy from inherited disease are to some extent protected. They are in a similar position to those who have passed through the acquired disease. This, however, is not the whole question. We have to ask whether the offspring of those who have recently had syphilis, but in whom no evidences of inherited taint have occurred, are yet in some degree protected? Can a parent, without transmitting the disease,

yet transmit a constitution in some measure immune? The affirmative may be held to be probable, and the degree of immunity may be supposed to be in direct relation with the shortness of the interval since the disease occurred in the parent.

Second infection usually results in the production of a much milder form of the disease. This is what occurs in cases of small-pox after vaccination, and after a previous attack of the true disease. It is surely impossible to believe that the constitution of a person who has passed through the stages of any of these diseases ever again returns to precisely the same condition in relation to the virus in question that it held before. It is equally inconceivable but that some share of this peculiarity shall be transmitted to offspring. A child born of parents neither of whom is liable to small-pox or to syphilis, as the case may be, must be in a different position, as regards those diseases, from the child of parents both of whom are liable. Now, it is a matter of well-proven observation that any specific disease will be especially severe when imported into a community previously free from it. The ravages of small-pox in a virgin race is something far beyond what is ever known in a community long accustomed to the disease. There are also some reasons for believing that during the last two centuries syphilis has become a milder disease than it was when it first invaded Europe. This amelioration we may explain by recourse to the hypothesis above suggested; [1] but in doing so it must be borne in mind that improved treatment may have had its share.[2]

Lastly, we have to ask the all-important question, *whether the ordinary evolution of syphilis can be altered in any way by measures of treatment.* It will probably be admitted that physicians have abandoned the notion that it is practicable by medication to regulate in any way the course of the other exanthems. They are generally acknowledged to be diseases which always run their course. No single specific in the present day

[1] This subject will be found very ably treated in Mr. Lee's *Lectures on Syphilis* (Lecture XI. p. 209). I published in the *British Medical Journal* some cases in which patients who had suffered from inherited syphilis subsequently contracted venereal sores. These cases were, I believe, the first facts relating to the subject which had been recorded. Others had arrived at the same conclusions, but it was by *a priori* reasoning rather than by deduction from observations. Subsequently I published a case in which a patient who was the subject of inherited taint not only contracted a venereal sore, but experienced an outbreak of constitutional symptoms. I recorded a number of observations bearing on this subject in the second volume of the *London Hospital Reports*.

[2] If we reflect on the mode in which syphilitic inoculation is usually effected, the wonder will be, not that apparent varieties both in primary and secondary symptoms occur, but that the disease is, as a rule, so uniform as it undoubtedly is. Here, if anywhere, are the conditions under which we might expect a new species to originate. In the first place the virus is constantly mixed with other secretions, and very frequently with those of inflammatory origin. In a great many instances the person from whom the contagion is received is one whose own body has been previously rendered to some extent proof against the disease. Most prostitutes probably suffer from syphilis early in life, and during the greater part of the period during which they continue their vocation are incapable of being themselves again infected by true syphilis, although still liable to contract and to transmit primary sores of a modified character. Further, not only must we make allowance for differences in the kind of secretion with which the inoculation is effected, but also for differences in the recipient's state as regards it. Hence the differences in the cutaneous rash which follows—from a roseola to psoriasis and to rupia.

enjoys any repute for cutting short the course of these diseases. But we must by no means assume *a priori* that the same will hold true as to syphilis. It is possible that the stages of the other exanthems are too short to permit of the beneficial influence of antidotes. Few questions in therapeutics have been more hotly debated than the efficiency of certain drugs in syphilis. By some their specific power has been positively asserted, by others as strenuously denied. When, in 1866, I wrote for Reynolds's *System of Medicine* the article on Syphilis upon which the present one is based, I recorded the opinion that it was not possible to prevent the secondary phenomena by mercury. During the years which have since elapsed, however, great progress has been made, and it is now justifiable to write that, if treatment be begun early and efficiently carried out, it is perfectly possible to suppress syphilis and to prevent the occurrence of any of the humoral group of symptoms. If mercury be begun as soon as the state of the sore permits of diagnosis, and continued without intermission in small but adequate doses, the patient will usually entirely escape the whole series of symptoms which constitute the secondary stage. He will have neither fever, eruption, sore throat, nor bone-pains. A most interesting and conclusive proof that the disease is really thus held under, as it were, by the drug, is derived from the observation that if the latter be left off prematurely an eruption will make its appearance about six weeks later. Such eruptions are, however, always very mild, and yield at once when the remedy is resumed. It would appear that, in many cases, a year's administration of the remedy, without any intermissions, is necessary to the permanent suppression of the disease. For twenty years past I have been practising this early and continuous method, and can speak definitely as to the uniformity of the results. The details of this treatment will come under consideration later; for the present I allude to the subject chiefly in order to emphasise the truth that we have in mercury a drug which is powerful to suppress the phenomena of syphilis and to change the course of their evolution. It is too soon to make any attempt to prove that patients so treated are less liable than others to tertiary affections, but so far my experience has been that they escape the class of phenomena grouped as "reminders" (the intermediate stage) and are to all appearance cured. It may not be out of place to remind the reader that under the older surgeons, who did not attempt any differential diagnosis of chancres, vigorous mercurial treatment was usually commenced at once, and mercury pushed to profuse ptyalism was, with many, the remedy for all forms of venereal sore at a very early stage. It is not improbable that in this somewhat haphazard manner success was not infrequently obtained in suppressing the disease entirely. There was, however, much risk of failure from the habit of giving large doses and very short courses.

Modes of Communication.—While the other exanthems are for the most part communicable only by direct contagion or infection to the individual concerned, syphilis, in consequence of its very protracted duration, may be conveyed in any one of four different modes. *First,*

contagion direct to the individual; *second*, contagion indirect through the fœtus (possible only in women); *third*, contagion from a mother, who acquires syphilis during her pregnancy, to a previously healthy fœtus; and, *fourth*, by sperm- or germ-transmission at the date of conception.

The period during which direct contagion is possible extends from the first appearance of the chancre to the end of the humoral or secondary stage. The primary sore is perhaps more actively contagious than are any lesions which may occur in the secondary stage, but there can be no doubt that under favourable conditions the disease may be conveyed by the latter. When syphilis is communicated to a mother by contamination from the fluids of a fœtus with which she is pregnant, the course of the disease is materially different from what it is when received by other means. As a rule the woman shews no symptoms during her pregnancy, and may appear to be in perfect health. This may happen in repeated pregnancies, and throughout there may be nothing to shew that the maternal fluids have been in any way contaminated. That they do, however, invariably receive some taint, is proved by the observation that such mothers never (with the very rarest exceptions) contract chancres from nursing their infected infants (Colles' law). They are protected. In many cases, however, such mothers do subsequently suffer from definite maladies more or less closely resembling those of the tertiary class.[1]

When syphilis is transmitted from parent to offspring various important peculiarities are observed in its manifestations. In the first place, the phenomena of the secondary and tertiary stages may seem to occur together; or at any rate we have a superficial rash on the skin resembling a secondary one, coincident with nodes on the bones and with deposits in the viscera. These cases are, however, exceptional; as a rule the stages occur as in the adult, the secondary rash disappearing after a few months, and a prolonged period of health intervening before the tertiary symptoms shew themselves. It is possible when severe disease of the bones or viscera, or both, occurs in young infants simultaneously with skin eruptions, that we ought to regard such lesions as being merely very severe secondary phenomena. Unless fatal they are transitory and very different from the chronic affections of the true tertiary class to which the subjects of inherited taint are liable in after years. The effect of the syphilitic poison upon the ovum is in many instances to destroy its vitality at an early period, and consequently to induce abortion. This, however, is far from being its constant effect. In the majority of such conceptions the tainted fœtus is carried to its full period. In

[1] I am aware that many cases have been published in which contamination from the fœtus was held to explain severe outbreaks of secondary syphilis. Without venturing to deny or even to doubt such a possibility, I may yet suggest that in many or possibly in all of these the primary sore had been overlooked. As regards the third mode we have no facts in proof that syphilis so acquired differs from that obtained by a fœtus at the date of conception. It is desirable, however, that we should keep in mind the possibility that there may be a difference. It is quite certain that a pregnant woman who acquires syphilis may and commonly does infect her fœtus, and that the infant born in such circumstances may suffer severely, and, I think, from the usual train of symptoms.

exceptional instances it is then brought into the world with manifestations of its disease already apparent; more usually this is not so, and the infant, which when a few weeks old will suffer most severely, appears at first to be perfectly healthy. In these infants a period of a fortnight to two months usually elapses, and then a rash appears, and the nostrils become stopped by swelling. At this stage the mouth is usually hot, its mucous membrane red and tumid, and the gums swollen. The child wastes, and assumes a shrivelled, senile aspect. Sometimes acute, well-characterised iritis occurs. Condylomas are frequently seen. The cutaneous exanthem may vary in character, much as it may do in the adult. Many children die during this evolution of secondary symptoms. If they survive, they usually in the course of a year get rid of all traces of disease, excepting perhaps an unusual pallor of skin, certain scars which may have been left on the face by the eruption, and an expanded nasal bridge caused by the long-continued swelling of the parts within.

I have said above that the tertiary and secondary stages sometimes appear to be strangely mixed in the early symptoms presented by syphilitic infants. Amongst the phenomena occasionally met with in these circumstances are nodes of the skull and long bones, and gummas of cellular tissue, of tendon, or of muscle. The liver, kidneys, thymus gland, and other parts, may also be attacked. Such children are certainly more liable than others to serous inflammations. Serous arachnitis to a slight extent is very common, and pleurisy is not an infrequent cause of death.

A condition of *severe anæmia* often results during the outbreak of early symptoms in a syphilitic infant, and from this death often results. In many cases, however, the child does not emaciate, but retains an appearance of good health which is remarkable considering the nature of the disease. I have often seen infants who were well grown, stout and strong in an unusual degree, who yet presented well-characterised indications of inherited taint.

In the child as in the adult the secondary symptoms pass away in due time, and a period of health or latency ensues, of variable duration; after which the later phenomena shew themselves. These are in part of the same character as those in the adult, but with the addition of several others which are not often met with in connexion with the acquired disease. There are few more remarkable points in the history of this most interesting malady than that the disease known as interstitial or syphilitic keratitis almost never occurs as a consequence of acquired disease; whilst it is common in the inherited form. I must also note here a remarkable exception to what has been stated to be the characteristic of tertiary symptoms in the adult, that they are but exceptionally symmetrical. It is a curiously difficult question to determine whether the late phenomena of inherited disease should rank as secondary or tertiary. Although it may seem almost absurd to claim inflammations as secondary which may occur twenty or thirty years after birth, yet there are certain facts which strongly suggest that this would be the most

correct method of arranging them. What we have hitherto counted as the tertiary symptoms in the inherited disease are very different from those of the acquired form. They are all almost invariably symmetrical, and they are all subject to the law of spontaneous decline. The persisting and aggressive forms of local disease, so common in the late stages of the acquired disease, are almost unknown in the subjects of inherited taint. Lupoid affections of the skin are the commonest form of tertiary acquired disease; they are almost never seen in that which is inherited. When keratitis of the interstitial form occurs in the subjects of acquired disease (very rare), it is always amongst the secondary phenomena: in the inherited disease it may occur very late, it is almost always symmetrical, and always transitory. It is invariably omitted from the phenomena of the secondary stage. No case, so far as I know, is on record of interstitial keratitis in an infant. The same is true of otitis, which occasionally leads to symmetrical deafness in subjects of acquired disease, but very often in those who inherit it. We have been so much in the habit of regarding persistent nodes as tertiary, that it is difficult to think of them in any other sense; yet, undoubtedly, in the acquired disease a general tendency to slight periostitis, usually symmetrical, is often observed in the secondary stage; and now and then large swellings are produced. These pass away, and after, it may be, a long series of years, we encounter the tertiary nodes which are asymmetrical, and which persist unless cured by treatment. Now in hereditary syphilis, although the osseous system often suffers severely, we rarely see anything resembling the tertiary kind of node. The tendency to periostitis is also transitory, and it does not recur in adult life. It ceases, too, irrespective of treatment. The gummas of the tongue which are so common in acquired syphilis are scarcely ever seen in the inherited form. It may, indeed, be asserted that there is very little to contradict the view that in inherited taint the secondary phenomena may be spread over many years, and that we have but little evidence of tertiary ones, parallel with those seen in the acquired disease. The explanation of this latter fact is perhaps to be sought in the more rapid and complete metabolism of tissue during youth and adolescence, by which the system is more thoroughly purged of all morbid material. It is not, however, to be doubted that in exceptional cases any and all of the tertiary phenomena which may occur in the acquired disease, may be met with also when it is the result of inheritance. All that is asserted is that they are comparatively very infrequent. In connexion with inherited taint we may see in the adult cases of chronic bone disease, of gummas, or of the degenerative changes in the nervous centres leading to general paralysis or tabes, but they are as rare as are examples of interstitial keratitis in the acquired form.

Conclusions as to the transmission of inherited taint. The following appear to me to be well established :—

1st, A child may inherit syphilis in a severe form from but one parent—from its father alone, or from its mother alone.

2nd, When both parents are the subjects of syphilis a child is more

certain to suffer, and is perhaps more likely to suffer severely, than when only one is infected.

3rd, We have as yet no data on which to base an opinion whether a child is more likely to suffer severely when its father is the source of contamination than when it derives the disease from its mother; or the reverse.

4th, In a large proportion of the cases met with in practice, the taint is derived from the father only.

In connexion with the hereditary transmission of syphilis, an exceedingly important question arises, *whether any degree of taint is transmissible to the third generation.* There is no doubt that persons of marriageable age often present heredito-syphilitic lesions in an active stage, such as keratitis and nodes. I have repeatedly seen patients of various ages, from twenty to eight-and-twenty, become the subjects of syphilitic keratitis for the first time. We might conjecture that such persons would be likely to transmit to their offspring some degree of taint, seeing that the taint is still in activity in their own bodies. I am not aware that any facts have as yet been published on this subject. Conjectures abound, and several surgeons have expressed their belief that the influence of syphilis once acquired is felt through several subsequent generations. About eight cases have come under my own observation in which persons, undoubtedly the subjects of inherited disease, have become parents. With one doubtful exception, I have never been able to discover any evidence of disease in the offspring. In several instances the offspring have appeared to be in excellent health. I have always made a point of seeing the children for myself, never relying upon the parents' statement—a precaution which is essential.

Quite recently a very instructive case has been under investigation at the Polyclinic. A woman bearing unquestionable evidences of inheritance, brought an infant which shewed equally unquestionable symptoms. For some time all history of acquisition was denied, but at the last moment it came out that the woman had, since her marriage, been under hospital treatment for sores on the genitals supposed to have been communicated by her husband. The child's inheritance was, therefore, probably paternal or from recent disease in both parents.

It is very important to realise that *during the secondary or febrile period of syphilis every tissue in the body is more or less affected* by the poison. Although we are accustomed to speak of sore throat, eruption, iritis, and so forth, as the secondary symptoms, yet in naming them we instance only those which are most conspicuous, and by no means all. Although in a majority of instances from first to last there may not be any indications whatever of general tissue-implication, yet we must accept it as proven that such is the case. The accidents which have happened in syphilitic vaccination, as well as many other occurrences, shew that during this stage of the disease the most minute quantities of the patient's blood, or of the serum secreted by an abrasion, may prove fully contagious

and produce the complete disease in another person. How soon this vital activity of the virus in the blood usually ceases, and how long it is possible for it to last, are very important questions to which as yet no definite answers can be given. That it does not last indefinitely, and that in a large majority of cases it ceases within a comparatively short period, say within a year or eighteen months, is made probable by a large body of circumstantial evidence. Syphilis in married life would be far more common than it is if this were not the fact. Thousands of men marry at or about the end of two years after primary syphilis, and many at much shorter periods; yet the instances of communication of the disease to their wives and children are but infrequent. On the other hand, if marriage take place within a year of the primary disease, it is perhaps exceptional for the children to escape, and by no means uncommon for the wife to acquire a chancre. What I have named for convenience the "*after-marriage chancre*," is a temporary abrasion occurring as the result of frequent intercourse immediately after marriage on the penis of a man who has formerly had syphilis. Of these I have seen several remarkable examples with their results of chancre and secondary syphilis in the newly-married wife. It seems to be possible that such sores may be produced at a period as long as two years after the primary disease, and in cases in which the man has long appeared to be quite free from symptoms. Fortunately they are extremely infrequent, and I may state that, although I have for many years been accustomed to allow marriage after the expiration of two full years, I have never in any single instance seen ill results in cases in which I had permitted it. For my present purpose, however, they suffice as proof that the virus of syphilis may live on in the patient's blood during the long period mentioned; and this, too, in some instances, in spite of much treatment by mercury. Their rarity, I repeat, may also be permitted to demonstrate the converse proposition that in a very large majority of cases the virus does not so survive. We may hope that important evidence on this point will result from Schaudinn's discovery of the *Spirochæta pallida*.

What has just been asserted as regards the general diffusion and possible persistence of the virus in the blood must be admitted also as a possibility in reference to all the viscera and all the tissues of the body. Putting aside as unquestioned the affections of the skin and mucous membranes, it may be well to say a few words respecting the nervous system and its appendages, the arterial system, and the bones.

Nervous System.—Fournier has taught us that in some cases in the secondary stage of syphilis the patient experiences a general loss of sensibility to pain in the skin. This curious condition he met with chiefly in young women who were much reduced in health. This class of patients has not been much under my own observation, and I am not able from my own experience to say much in corroboration of the statements of this distinguished observer. That symptoms of nervous disturbance, sometimes local and sometimes general, do, however, occur in the secondary period of syphilis, there can be no doubt. I have seen and recorded a few instances

in which a state of general paralysis involving both motion and sensation occurred, and the patient was apparently saved from impending death only by the very prompt use of mercury. In another very important group of cases the spinal cord appears to be the seat of myelitis in its lower part only; and a temporary condition of paraplegia, which may be almost absolute as regards both sensation and motion, and which involves the sphincters, may be established. In some of these cases the upper extremities are more or less involved also, but usually they escape. The paraplegia is generally symmetrical, though not always. A very remarkable corroboration of the diagnosis which traces this affection to a temporary inflammation of the secondary type is obtained from the observations that it is usually curable by vigorous treatment, and that once cured it shews no tendency to relapse. In these features it corresponds with what we know of the otitis, iritis, and other affections of the secondary stage, which are probably its analogues. It may be noted also that it differs widely from the tertiary affections of the nervous system, which are usually aggressive, and which tend to relapse after apparent cure. Inflammations of the sense-capsules—the eye and the ear—although exceptional, are not very rare in the course of secondary syphilis. They are usually acute and transitory, but unless very promptly treated may result in much damage to the organ. Affections of single nerves, as denoted either by paresis or by very severe pain, may occur in almost any region during secondary syphilis, but they are rare.

That the *osseous system* is implicated during the secondary stage, is often proved by the presence of what are called "osteocopic pains" or "syphilitic rheumatism." These pains are not very infrequently accompanied by local periosteal swellings of the most definite character, but differing from our ordinary conception of a node in that they are very transitory, never tend to suppurate, and leave no perceptible thickening behind them. They are sufficient, however, to prove that periostitis does occur during the secondary stage.

If we turn to the *arterial system* we find facts of the utmost importance, although somewhat difficult of interpretation. It appears probable that in many if not in most cases of syphilis the whole arterial system suffers more or less during the earlier stages, and that certain changes take place in the arterial coats, more especially in the intima, from which the recovery may never be absolutely complete. The arteries may remain through life liable to take on other forms of disease, under the influence, it may be, of local exciting causes; hence aneurysms, thrombosis, endarteritis obliterans, and their results in hemiplegia and other forms of paralysis. It would appear probable that at various stages of syphilis it is possible for a single arterial trunk to become involved in changes which produce a considerable narrowing of its calibre and a corresponding diminution of the supply of blood to its territory. In interpreting some of the phenomena of nervous disturbance, it is often extremely difficult to say whether they are primary to the nerve-structures themselves or only secondary in consequence of arterio-capillary disease. There

yet remains much for the pathological anatomist to elucidate in this matter.[1]

Tertiary Symptoms or Sequels.—I have endeavoured to draw a fairly strong line of distinction between secondary and tertiary manifestations. The secondary phenomena constitute a stage; they come on at a certain known period; they are in their nature transitory, and disappear spontaneously; they affect the two halves of the body at the same time, proving that they depend upon blood-poisoning; when once passed they rarely return. The tertiary symptoms are not so properly a stage, but must count rather as the sequels, more or less accidental, of the preceding stages. They are as a rule not symmetrical, a fact which makes it seem improbable that they depend upon blood-taint; they have no tendency—but quite the reverse—to spontaneous cure. They relapse over and over again after remedial treatment. The period which intervenes before their outbreak is of very different length in different cases, and in many they never occur at all. From these considerations we infer that they are due rather to the altered constitution of the affected structures than to any free virus still circulating in the blood.

We may briefly enumerate the principal tertiary symptoms as they occur in relation to special organs or structures. Tertiary affections of *the skin and mucous membranes* differ in a most marked manner from those which occur in the secondary stage. With the exception of palmar psoriasis, and a few others, they usually result in ulceration of greater or less depth, and consequently leave cicatrices. Very frequently the patch assumes a crescentic form, spreading at its edges and healing in its centre,—the well-known "horse-shoe" or serpiginous ulcer. If the disease begin in the middle line it may spread equally on the two sides, and may thus appear to be symmetrical; but it is decidedly unusual for symmetrically placed patches to appear on the opposite limbs, or on corresponding parts of the trunk. In many cases the skin is invaded secondarily to the subcutaneous cellular tissue, the disease having begun as a gummatous tumour or node of the cellular tissue. A form of lupus attended by rapidly spreading phagedænic ulceration occasionally occurs in tertiary syphilis; but there is good reason for believing that the common forms of lupus, whether exedens or non-exedens, have no connexion whatever with syphilitic taint. The appendages of the skin, the nails and hair, which are frequently affected during the secondary stage, but rarely suffer at later periods.

The most frequent affection of the mucous membranes which we encounter in connexion with tertiary syphilis is a rapidly spreading

[1] We are indebted to Dr. Bristowe for some of the earliest and most trustworthy investigations in reference to the disease of the arteries in syphilis. In Germany A. Wagner was one of the pioneers. Dr. George Oliver, in the course of his researches on arterial pressure and variations in the calibre of arteries in different positions, came upon the very remarkable observation, that in the subjects of syphilis (in all stages) the radial artery continues uniform in size in the erect and recumbent postures. This he found so constantly the case that it was impossible to attribute it to local or exceptional disease. He believes that it indicates some change in the arterial coats of such a nature as to elude recognition by the finger, which cripples the physiological play of the tube.

ulceration of the palate and pharynx. This, again, is totally different from the throat affections which occur in the earlier stages. Instead of being superficial and marked chiefly by swelling and inflammatory deposit, it is characterised by deep ulceration and loss of tissue. Instead of shewing itself symmetrically on the two sides, it commences at one, two, or more points, and spreads quite irregularly. The scars left by these deep ulcerations not infrequently narrow the pharynx and occasion difficulty in deglutition. In a few cases the ulceration may extend down the œsophagus, and in many the larynx is involved. Every now and then we see cases of tertiary syphilitic ulceration of the mucous membrane of the rectum, and again we must note that it is ulceration, and that it is not attended by the development of the condylomas or mucous patches of secondary syphilis. Stricture of the rectum is much to be feared when these ulcerations heal. Several authors have described cases resembling dysentery in all their symptoms, but occurring in syphilitic patients, and cured by antisyphilitic remedies. Sir James Paget recorded a case of this kind, and I have myself seen some very well-marked examples. It is probable that in such cases ulceration of the mucous membrane is present at a considerable distance above the anus. I have seen several cases in which it extended above the reach of the finger.

The cellular tissue is frequently involved in common with muscle, with periosteum, or with fascia. In not a few cases, however, we meet with what are called cellular nodes, in which the disease begins and is, up to a certain period, confined to the areolar tissue. These may occur in any part of the body, but are much more usually met with in the lower extremities than in any other part. They are very common near to the knee, and especially so in women.

In the early stage of a cellular node we find a small lump of induration which is often exceedingly tender. At first it is firm, but as it extends it becomes doughy and softer. When of considerable size there is frequently a very deceptive sense of fluctuation in it. The overlying skin becomes adherent and of a dusky red colour. At length ulceration takes place, and a large core is exposed, consisting of sodden and infiltrated tissues, much resembling soaked wash-leather in appearance. Unless specific remedies be used, this core is very slow in separating, and the ulceration of the skin over it may spread widely.

Cellular nodes are not infrequently multiple, but more usually single. The patient frequently has scars of former ones on the opposite limb, but it is exceptional to find them simultaneously present on corresponding parts.

A period varying from four to ten or fifteen years has usually elapsed between the occurrence of primary contagion and the development of cellular nodes. In close connexion with syphilitic inflammation of the cellular tissue we must mention that of *subcutaneous bursæ*. It is not at all uncommon for a bursa to suffer in connexion with the disease of the tissue around it, and sometimes there appears to be clear evidence that the disease began in the bursa itself. The bursa in front of the patella is the one most frequently involved.

The joints themselves may be occasionally implicated in tertiary syphilis. Usually they are involved secondarily, in connexion with periostitis of the bones which form them. In the secondary period rheumatoid pains in joints are common, and in inherited syphilis symmetrical effusion into the knee-joints often coincides with the keratitis: in such circumstances the joint affection is always transitory, and it may be plausibly suspected that it is the result of direct humoral infection from the inflamed corneal tissue. Chronic affections of joints in the tertiary stage of syphilis, and in connexion solely with it, are exceedingly rare.

Inflammations of the periosteum and bones have long occupied the most prominent place amongst the tertiary symptoms of syphilis, and they are still amongst the most common. In enumerating the symptoms which characterise the secondary stage we have mentioned pains in the bones, occasionally attended by slight and temporary swelling. This kind of periostitis, however, never lasts long, and, so far as my own observation goes, never leads to suppuration. Tertiary nodes seldom occur until at least two years have passed since the first contagion, and generally the interval is much longer. They may affect almost any part of the osseous system; but the bones which are superficial, and therefore most exposed to external influences, are those most frequently attacked; for example, the skull, the tibia, and the clavicle. The bones of the palate, the alveolar processes of the maxillas, the vomer, and other bones in the nasal passages, are very frequently affected; and when such is the case exfoliation of portions usually occurs.

Syphilitic periostitis may vary considerably in its degree of severity and in its tendencies. In some cases there is but little acute inflammation, and the result is a great thickening of the bone affected, without the occurrence of suppuration. This frequently occurs in the bones of the skull—the whole calvaria acquiring greatly increased thickness and density. It is also not uncommon on the surface of the tibia and other long bones, constituting what is known as the osseous node. In other cases softening occurs, and in these very frequently large portions of cellular tissue become involved, and we have a swelling consisting in part of a periosteal abscess and in part of a cellular node. When the bone is exposed by ulceration, exfoliation of portions often results.

When the bones of the skull are attacked by syphilitic periostitis, it is very possible that inflammation may occur internally as well as superficially, and that we may have symptoms referable either to irritation of the cerebral coverings or to compression consequent upon intracranial abscess. In association with nodes on the skull various symptoms of mental disturbance may shew themselves: extreme irritability of temper, liability to fits of uncontrollable passion, melancholia, and even acute mania may occur. These symptoms of mental disturbance may or may not be associated with those of local paralysis. They not infrequently result in attempts at suicide. The proof that they really are dependent on syphilitic lesions is afforded by the ease and rapidity with which they

are relieved by the iodide of potassium. Periosteal nodes are not very frequent on the short bones; we must, however, be prepared to recognise them occasionally. The patella and the os calcis are sometimes affected, and now and then the other bones of the tarsus or carpus.

Diseases of the muscular system occur chiefly amongst the more remote sequels of syphilis, and they are by no means frequent. They usually take the form of nodes, or gummas, in the substance of some single muscle. The induration is usually very considerable, and in many parts abruptly limited. The diagnosis from malignant growths is often very difficult, and many mistakes leading to unnecessary operations and to supposed permanent cures of cancer have occurred. The muscular substance of the tongue is the structure most frequently attacked by this form of gummatous growth, but it has been met with in almost all the muscles of the body. The sterno-mastoid, the masseter, the supra- and infra-spinatus, the gastrocnemius, and the rectus femoris may be especially mentioned. Some forms of syphilitic indurations of the tongue are in all their stages exceedingly difficult to distinguish from carcinoma. They are very hard, have well-defined edges, are painful, and when they ulcerate present an unhealthy surface. Iodide of potassium in full doses will usually clear up the diagnosis in the course of a week or ten days. The heart itself is sometimes the seat of syphilitic nodes. Of this, Ricord [1] was, I believe, the first to publish an example; but many others have been recorded by subsequent observers.

The Glandular System.—Chronic enlargements of the lymphatic glands, sometimes resulting in suppuration, are every now and then met with as the sequels of syphilis. It is remarkable in reference to tertiary syphilitic lesions generally, that they do not cause any secondary enlargement of the adjacent lymphatic glands. This is true of syphilitic ulcerations of the skin and mucous membranes, of all the various forms of node, and of syphilitic tumours in muscles; and it often constitutes a very useful means of differential diagnosis between cancer and syphilis.

The Internal Viscera.—The investigations of modern pathologists have fully confirmed the conjectures of the older writers on syphilis as to the frequency with which the viscera of the trunk, and more especially the liver, suffer in constitutional syphilis. In connexion with this subject we must especially mention the very valuable contributions of Sir S. Wilks. As to the exact period in the course of the disease at which the viscera are attacked, it is difficult to obtain any positive evidence. What we discover in the post-mortem examination is usually the result of long past disease, and it is comparatively infrequent to find such affections in a recent stage. What evidence we have, however, favours the belief that it is not usually until the later periods that the viscera suffer severely.

The liver appears to be far more frequently affected than any other organ. Indeed, in the examination of the bodies of those who have

[1] See *Traité complète des Maladies Vénériennes*, Planche xxix. In this instance the patient was a man aged 41, who had suffered from a chancre followed by constitutional symptoms eleven years prior to his death.

suffered severely from tertiary syphilis, it is decidedly exceptional not to find some proof of hepatic mischief. The most common condition consists in large white patches of fibroid thickening on the surface of the organ. These patches are evidently cicatricial. The liver is knotted and puckered up by them, and cicatricial bands dip from the surface into the substance of the organ. Sometimes, when the destruction has been great, the whole bulk of the organ is diminished. In recent disease the affected parts of the organ are enlarged, and on section exude a glutinous and gummy material not unlike beeswax. I am not aware that abscesses have as yet been met with in the liver in supposed connexion with syphilis. Virchow recognised two forms of disease—a capsular hepatitis and an interstitial hepatitis. Of these the capsular inflammation is the more common and the less serious. It is probable that the two are generally associated to a greater or less extent. Ascites occurs every now and then in connexion with syphilitic disease of the liver.

Testes.—Syphilitic sarcocele has usually been classed by authors as a secondary symptom. I feel sure, however, that this is not quite correct. It is amongst the earlier of the sequels, but it very seldom occurs during the secondary stage. It is commonly met with in conjunction with nodes, and with deep ulceration of the skin rather than with the superficial rashes of the secondary epoch. It consists in the free effusion of lymph (fibro-plastic material) into the substance of the testis, or, more rarely, into the epididymis.

The swelling often attains a very considerable size, and when it does so it presents the peculiar feature of feeling very light in the hand. Syphilitic sarcocele is much more frequently symmetrical than any other form of tertiary syphilis. This circumstance we might expect from the fact that it occurs much nearer to the secondary stage than do most of the others.[1] Still, however, it is only exceptionally symmetrical.

Nervous System.—I have previously adverted to the occasional occurrence of cerebral symptoms in connexion with syphilitic inflammation of the bones of the skull, and to the formation of intracranial nodes; but, quite apart from disease of its osseous case, the brain itself may suffer directly from the formation of tertiary syphilitic deposits in its membrane, and yet more frequently from disease of its blood-vessels. There may also be deposits of like nature in the substance of nerve-trunks, producing special forms of local paralysis. To these isolated deposits the name "syphilitic neuroma" has been given, and many well-authenticated cases are on record in which the diagnosis has been confirmed by an autopsy. In a far greater number of cases the diagnosis has received an almost equally valuable confirmation in the cure of the disease by iodide of potassium. So frequently, indeed, is tertiary syphilis the cause of paralysis, that investigations in this direction ought never to be omitted in cases in

[1] On this point Curling wrote, "Sir A. Cooper thinks that in the majority of cases the disease attacks both testicles. The eight examples recorded in his work do not, however, bear out this remark, for in only two of them does it appear that both organs were attacked. According to my observations the disease is more commonly confined to a single gland, though it occasionally affects both; and this also appears to be the opinion of Ricord."

which the nature of the disease is in the least doubtful. It is, indeed, safe to go farther than this, and to say that in all cases of paralysis without evident cause, and in which syphilitic antecedents are even possible, it is advisable to try the effect of iodide of potassium. I allude chiefly to cases of paralysis of the cranial nerves, for it would appear that neuroma is more frequent in them than in the spinal nerves.

Syphilitic affections of the nervous system may occur in any stage; they are often among the late tertiary phenomena.

Amongst the most frequent of the affections of the nervous system following syphilis we are obliged to place tabes or locomotor ataxy. This affection may assume various modifications, and it often, indeed usually, occurs in those who shew no other indications of taint. It is probably of a degenerative character rather than inflammatory, and may be suspected to be due to changes in the arterio-capillary systems. Specifics have but little influence on it. Syphilis probably plays the part of a predisposing rather than an efficient cause. It leaves the spinal centres vulnerable, but does not bring about any active changes. The exciting causes are probably over-exertion, exposure to cold, and above all sexual intercourse. A far more serious malady, but fortunately much less frequent, is general paralysis of the insane. There can be no doubt that it is usually preceded by syphilis, and it is attended by inflammatory changes. It is also in many cases under the influence of specifics. These should be freely and constantly used. The exciting causes are intemperance, excitement, and sexual excesses. Tabes and general paralysis of the insane are to be regarded not as syphilitic but as para- or meta-syphilitic affections.

[For Tabes and General Paralysis of the Insane, see special articles in section on Diseases of the Nervous System, Vol. VII.]

Colles' Law.—About the year 1837 Mr. Abraham Colles of Dublin published the important observation that mothers who suckle their own syphilitic infants do not contract chancres on their nipples. If, on the other hand, a healthy wet-nurse be employed to rear a tainted child, a nipple chancre, to be followed by constitutional syphilis, is not an infrequent result. Subsequent observers have almost unanimously confirmed Mr. Colles' statements of the facts, although, as might have been anticipated, a few exceptions have been recorded. Preferring to give weight to these exceptions rather than to the great mass of confirmatory evidence, some have even suggested that what has been called Colles' law is at the most of but doubtful force. They contend that chancres of the nipple in wet-nurses are very rare, and those which occur in mothers not very infrequent; so that in reality no great difference between the two classes can be proved. This argument, will, however, be seen at once to have no validity when we remember that it is extremely rare for a wet-nurse to encounter risk, whilst for mothers to do so is an everyday occurrence. If mothers were in as much risk as wet-nurses we should see chancres of the nipple very frequently indeed. A surgeon who was responsible for a wet-nurse giving her breast to a syphilitic child would, if syphilis ensued, become

liable to an action for damages. No well-informed medical man ever does permit such a thing, and the number of cases in which healthy wet-nurses spontaneously give their breasts to infants with syphilitic mouths must be very small indeed. We may then assume that what has been called Colles' law does express a well-established and very important clinical fact.

It follows from Colles' law that a woman pregnant with a syphilitic child does receive from the fœtus something which renders her immune to the contagion of the disease. It is, however, most certain that in the course of her acquisition of this immunity she but rarely exhibits any well-marked secondary symptoms. It is common for a married woman to bear a tainted child, she having been, through her whole pregnancy and before it, quite free from obvious symptoms. We have proof, then, that the blood transference which occurs between fœtus and mother may produce immunity without causing any obvious outbreak, and this is a very important observation. To what extent such mothers are liable in the future to phenomena of the tertiary class is a question which it is very difficult to answer. That they do so suffer, not infrequently, seems to be well established; and is a corroboration of the belief that they do really receive infection during pregnancy.

When a man who has suffered from syphilis, but who believes himself cured, enters into marital relations with a healthy woman, the latter encounters risk of two different kinds. It may happen that a new excoriation on the penis may be produced, and that it may cause a chancre in the woman. In such a case all the usual phenomena of syphilis will probably in due course ensue. If this risk be escaped, it is not probable that the woman will suffer in any way unless she become pregnant. There is no reason to suppose that syphilis, with the rarest exceptions, can enter the system without a primary sore, or that the semen, or other secretions of the husband, can convey it. The second kind of risk will be encountered if the wife become pregnant. Whether it be possible for a paternally tainted fœtus to produce in its mother a severe outbreak of secondary syphilis must be held to be doubtful. Many cases are on record supposed to be examples of such occurrence, the wife having shewn abundant evidences of blood infection during the early months of pregnancy. In all such, however, there is the fallacy that a primary sore may possibly have been overlooked. On the other side cases are innumerable in which a young wife remains in perfect health, never manifesting the slightest indication of disease, and yet bears an infant destined to shew it. The latter is certainly the rule, and the former, if it ever occurs, is the exception.

A few words may be suitably inserted here as to the possibility of a mother who acquires syphilis during her pregnancy communicating the disease to her fœtus. The facts which have been recorded are to my own mind quite conclusive on this point. At whatever period of pregnancy the disease is so acquired up to the last four weeks, it is almost certain that the fœtus will be infected. So far as facts yet recorded

permit an opinion, no difference will be observed in the phenomena displayed by the child from those of ordinary inherited syphilis.

Syphilis in Reference to Marriage.—Before proceeding to discuss this question, I may at once aver my conviction that a great amount of human happiness is frustrated by the exaggerated fears which are entertained by the profession and the public. Not only are marriages needlessly deferred or altogether prevented, which had they been permitted would have produced only mutual good and blessing, but, on the other hand, unhappy and immoral connexions are greatly multiplied. When a young man is forbidden to marry because he has had syphilis, or when his own fears or what he calls his "sense of honour" prevent him, it does not by any means follow that he will lead a continent life. We have but to look at the subject in the aggregate to see how important are its bearings. It may seem but a little thing in an individual case; but what we have to remember is that syphilis in young men is and always will be very common, and that the cases are really very numerous. If we suppose a thousand young men otherwise wishful to marry, and in circumstances to do so with prudence, deterred from it by the fear of syphilis, we must realise that an equal number of young women must also at the same time lose their chance of marriage. Now, supposing that a period of two years has been passed since the primary disease in the man, the amount of risk which is run is probably infinitesimally small. That there is still some little risk no one acquainted with the facts would be prepared to deny. Shall we on account of that little danger at once lengthen the period to three, four, or five years? I believe that to do so would be to act unwisely. In this matter the profession should take the part of the reassurer and not of the alarmist. The fears of the public are far in excess of what the facts warrant. Many marriageable men, for whom marriage would have been perfectly safe, yet remain bachelors for years, or perhaps for their lives, from the consciousness of having had syphilis. If a similar degree of scrupulosity were to be observed in reference to the risk of transmitting tuberculosis or scrofula, or the neurotic diathesis, or that of arthritis or of cancer, we should have but few marriages. Yet the physical evils and suffering produced by the inheritance of these maladies far exceed those which result from syphilis. Compared with them, inherited syphilis is both rare and easily curable, and were it not that a certain stigma attaches to it as a "foul disease," and one for which the parent is morally responsible, it would receive but little attention.

In past years those who had suffered from syphilis were allowed to marry as soon as all symptoms had disappeared, and often within a very few months of the primary disease. Inasmuch as there is no reason to believe that infantile syphilis was much more common then than now, we may believe that in many instances a period of six months is quite adequate to free a man from the risk of begetting a syphilitic child. We know that in a large proportion of cases the patient himself becomes permanently free from manifestations within that period; and this consideration may help us to the belief that the virus does really perish from the blood so as to make

transmission impossible. It must be admitted, however, that in very many others it lingers much longer. The rule which now prevails widely of forbidding marriage for two full years from the date of the primary sore is probably a safe one. It may possibly be relaxed occasionally under exceptional conditions when the symptoms have disappeared very early and very completely; and there may be others in which the converse has been the case, in which a yet longer period should be required. It would, however, be a pity to make the general rule insist on more. It is foolish to concentrate our attention on a few exceptional cases and to forget the lessons taught by the vast majority. If the patient during almost the whole period have been efficiently treated with mercury, the absence of risk may be asserted with the greater confidence; but we must always remember that time as well as mercury cures syphilis. There are facts which seem to make it probable that the risk of transmitting syphilis to offspring lasts much longer in women than in men. When after marriage only the first-born child or the first two shew signs of taint, it is probable that the inheritance is from the father only. Whenever, however, a succession suffer, whether continuously or with interruptions, then it will usually be found that the mother has been affected. There is probably nothing inconsistent with physiological law in the supposition that specific poisons may linger longer in a latent state in the ova than in any other of the body-tissues, and clinical observation would certainly suggest that such is the case. A woman known to have had syphilis often bears healthy children, but there are facts on the other side which should lead the medical adviser to speak with great caution on the matter.

Treatment.—Respecting the treatment of syphilis a few general principles may easily be advanced.

In the first place, it is quite certain that all its early phenomena have a definite tendency to spontaneous disappearance. It is upon this well-established fact that the non-mercurialists build their hopes, and by which they have been able to claim for their opinions a certain amount of clinical support. The chancre, however large and however hard, will in time melt away; the hardened glands and the skin eruption will also disappear. In a majority of cases these primary and secondary phenomena will not assume any great severity, and the patient will never be seriously ill. It is, perhaps, in not more than half or even in a minority of cases that the disease assumes any serious features. In those in which it does so, the degree of severity will vary within very wide limits, and in a certain small proportion the severity of the fever, eruption, and other symptoms may be such as to endanger life. In some also we know that the secondary stage will never wholly disappear, but will pass on into conditions characteristic of the later one.

A second general proposition is, that over all the early manifestations the mineral mercury, in whatever form it may be introduced into the system, exercises a specific influence. It causes the induration of a chancre to disappear and the sore to heal, it makes the eruption vanish, it brings

down the febrile temperature if such have been present. The details of its influence will vary with the modes of its administration and the idiosyncrasies of the patient, but about these main facts there can be neither doubt nor dispute. The determination in detail of its influence on the life of the spirochæta is awaited with the utmost interest, and may prove most valuable.

Our third proposition is that over the tertiary manifestations of syphilis—the gumma—whether of skin, cellular tissue, coats of artery, cerebral meninges, or periosteum, the iodide of potassium exercises almost as definite an influence as does mercury over the earlier ones. Under its influence large gummas will disappear, periosteal pains will cease, and ulcers will heal.

Whether any other drugs, mineral or vegetable, exercise any specific influence over syphilitic processes is as yet not proven. It may be held as scarcely likely that mercury and the iodides are the only remedies which possess such powers; but although much has been from time to time asserted, nothing beyond what has been just stated has received the final imprimatur of professional experience.

In the discussion of details it may be convenient to take the last of our statements first. All are agreed that in the tertiary stages the iodide of potassium must be used. Since its introduction, indeed, the terrors of this stage have to a very large extent vanished. The iodide should be given in doses suited to the idiosyncrasy of the patient and the resistance of the malady. There is no remedy in which idiosyncrasy counts for so much and in which the dose may vary within such wide limits. It is well to begin with small doses, invariably to combine ammonia with it, and to increase the dose only if required. Sometimes minute doses, of a grain or even a third of a grain will exercise as definite a curative influence as thirty times the quantity may do in another patient. It is, as a rule, not well to give it long continuously, but to omit it for a few days at a time, and to begin anew with a smaller dose. In cases of idiosyncrasy, in which it exercises an injurious influence, and brings out eruptions or causes œdema of mucous membranes, all that is needed is to reduce the dose sufficiently. In many cases the three iodides, of potassium, sodium, and ammonium, may suitably be combined. Whether these salts be given together or not, in no case must the addition of ammonia be forgotten; it is reputed, and with reason, to double the effect of the dose. Iodide of potassium has for many persons heavy drawbacks. At the same time that it cures the syphilitic lesion it often depresses the general tone, lowers the spirits, and entirely incapacitates the patient for the enjoyment of life. Indiscriminately used, as it is by many at the present time, it is productive of much wretchedness, which might, by a little care, be avoided. It is well in almost all cases to combine nux vomica (or strychnine) with the iodides, and in cases in which pustular eruptions are produced to give arsenic. Iodoform, given in doses of five to ten grains and in the form of pill, is sometimes better borne than any of the iodides. The local use of the iodides for all local and external tertiary affections might with advantage

be resorted to much more frequently and freely than is usually done. Lotions of iodide of potassium applied as a water-dressing under oiled silk, ointments of iodoform, iodol, or of chinosol are often much more efficient than their internal administration and less open to the risk of ill consequences.

The use of mercury in syphilis has been the subject of almost endless debate and difference of opinion. It may be given in very various methods and in very different doses. In order to avoid prolixity, I will begin by describing in a little detail the plan which I think by far the best, namely, that of the continuous use of small doses over long periods. By it, if begun early enough—that is, before the appearance of secondary symptoms—the evolution of the disease may be wholly averted, and not a single symptom beyond those of the primary stage may be allowed to appear. It is difficult to conceive any better result than this. The preparation which is the most easily managed is the grey powder (hydrargyrum cum creta), and there are obvious advantages in keeping as much as possible to one form. The dose should, as a rule, be one grain only, given in pill in combination with opium, and repeated as frequently as the patient can bear it. It is most important to begin with sufficient opium, so as to be secure against diarrhœa at the onset. A fifth or even a fourth of a grain in each pill is not too much. Should it cause headache, drowsiness, or constipation it can easily be reduced. The two complications to be avoided are salivation and diarrhœa. The problem is to introduce as much mercury as possible without the occurrence of either of these. The diarrhœa is to be prevented by opium and attention to diet; the salivation by frequent cleansing of the teeth and the use of an alum mouth-wash. The pill suggested should be given four, five, six, or seven times a day without regard to meal-times. On no account should the patient be allowed to take two together; by dividing the doses inconveniences are avoided, and the desired effect produced with much greater certainty. All soups, green vegetables, fruit, and malt liquor should be strictly forbidden. The patient should be advised not to smoke, and should be told that he will have to carry out the treatment for twelve months without any intermissions. In very few cases will it be found desirable to make the dose of mercury larger. As a rule Dover's powder appears to be more effective in preventing diarrhœa than its equivalent of opium.

An experience of many hundred cases treated according to the above plan justifies the statement that if it be faithfully carried out syphilis may be wholly suppressed, and the patient may never know anything about his malady beyond its primary symptoms. In many cases he may come to doubt the diagnosis on account of the rapidity and completeness of his cure.

Some very curious facts have been observed in connexion with this continuous treatment with the object of suppression. If at the end of four or five months, during which the suppression has been complete, the mercury be left off, there will usually appear at the end of a month or

six weeks a very definite secondary and symmetrical eruption. It will, however, be a very slight and mild one, and will disappear very quickly when the remedy is resumed. Of the secondary symptoms, sores on the tonsils are those most difficult to prevent; and many patients who wholly escape eruptions yet shew a slight form of the characteristic sore throat. This may be because the throat usually suffers very early; or it may be that mercury is occasionally the cause of congestion of the pharynx. During the course of treatment suggested the patient need take no special precautions. He may live as usual and follow his avocations. The more closely he keeps his house and the longer the time that he spends in bed the less will be the quantity of mercury required. Ptyalism, if it occur, must be regarded as an accident, and not in the least as proof that enough mercury has been given. It must be remedied as promptly as possible, kept at bay by constant cleansing of the mouth and teeth, and the mercury, in reduced doses, must be continued.

The efficacy of mercury in the treatment of syphilis is so well assured that all modes of use can claim triumphant results. The relative advantages of inunction, hypodermic injections, and administration by the mouth may perhaps be fairly summed up as follows: To those who hold that the treatment should be not interrupted but continuous over a long period, the mouth method is the only available one. Inunction is so disagreeable, and injections not only so disagreeable but so expensive, that the patient is almost sure to shirk both one and the other as soon as his symptoms have well disappeared. To a very considerable proportion of patients neither of these methods is, for various reasons, available, whilst to none, with but few exceptions, have they any real advantages over their competitor. The exceptions occur in the case of careless or reluctant patients who cannot be trusted to take their medicine regularly. These are chiefly met with in the services, and for such the hypodermic syringe has its advantages. In behalf of the continuous small-dose administration by the mouth, it may be alleged that it has been abundantly proved that it will effect the removal of syphilitic symptoms in all stages just as quickly as either of the others, that it does not interrupt the patient's avocations, that it causes no inconvenience, and is economical. All that is necessary is to guard the mercury efficiently with Dover's powder, and to explain to the patient that the course is to be a long and continuous one, and that the rules, detailed above, as to diet and so forth are to be rigidly observed.

During the treatment the patient will lose fat but not flesh. He will retain his strength, but may fall a little in weight. At the end of it he will probably declare himself in better health than ever before in his life.

In certain circumstances, but not often, it may be well to combine iodide of potassium with mercurial treatment in the secondary stage of syphilis. This will be the case if the bone pains are severe or if the mucous membranes suffer severely. Provided, however, that the mercury have been begun early enough, such symptoms will seldom occur.

It has seemed best to state the ordinary result of the suppressive

treatment by mercury before considering whether mercury ought or ought not to be used. If the statements just made are well founded there can hardly be a doubt about it, since the advocates of abstinence from specifics cannot but admit that, although many patients do well, many others suffer very severely. The same remark applies also to other methods of using mercury, for of none can it be alleged that less trouble, or less expense, or less risk of loss of health to the patient is involved. Better results could not possibly be obtained. Whilst, therefore, it is to be admitted that the inunction-method, that by subcutaneous injections, and that by the vapour bath, are all of them exceedingly useful, it is yet difficult to find advantages in any of them over that recommended. The estimation of the results of treatment in syphilis has two aspects: first, the prevention of inconvenience and loss of health during the secondary stage; and, secondly, the prevention of sequels and of tertiary symptoms. That, in regard to the former, mercurial treatment is triumphant there can be no reasonable doubt. It is, however, a very different thing and much more difficult of accomplishment to prove that it is influential in avoiding the latter. To do this, it is needful to collect indifferently the case-histories of many patients extending over the whole life subsequent to the attack. Whilst, however, it may be admitted that no plan of treatment, however successful at the time, can be held to secure the patient against subsequent risk, there is much to be said in favour of the belief that it is a decided gain to suppress, or, if too late for suppression, quickly to cure the secondary stage. Many facts favour the belief that gummas usually appear in the sites of former syphilitic lesions, and if so, it must be a gain to prevent the development of the latter altogether. Further, nothing is more certain than that those who suffer severely in the secondary period often do so also in the later ones. All the cases of so-called "malignant syphilis" are instances of a severe secondary stage imperfectly combated. Under the suppression plan none such, unless in connexion with very exceptional idiosyncrasy, ever occur.

Laborious attempts have been made to bring to statistical test the decision as to whether mercurial treatment is useful in preventing the occurrence of tertiary symptoms. Such an inquiry is, however, surrounded by fallacies. So much depends upon the precise details of the mercurial course, and still more upon the stage of the disease at which it was commenced. The conclusions of those who have conducted the inquiries are, however, I think, in accordance with *a priori* probability; and the impressions derived from such experience as I have had are to the effect that efficient mercurial treatment in the early stages is very efficacious in the prevention of remote sequels. For myself I attach the utmost importance to what I have ventured to call suppression treatment, that is, treatment begun before the development of secondary symptoms, and having for its aim their entire prevention. To begin with mercury very early and to continue it very long seems by far the most hopeful method of prevention of tertiaries.

Diagnosis of Acquired Syphilis.—The recognition of syphilitic symptoms in the *secondary stage* is not usually difficult. The copiousness of the rash, its symmetry, the copper-tint, the frequent coincidence of different types of skin eruption in the same case, the presence of febrile disturbance, the absence of cutaneous irritation and the co-existence of sores on the tonsils—and frequently on the mucous membrane of the cheeks also—are all features which help to make the diagnosis easy and certain. To these we may add that the syphilitic exanthem usually appears first on the abdomen, chest, and fronts of the arms, that it very commonly affects the face, and that it avoids the backs of the elbows and the fronts of the knees, localities which are almost always attacked in cases of common psoriasis. The patient's genitals and groins should always be examined, for in the early stages of the secondary eruptions it seldom happens that all traces of the primary symptoms have disappeared; often these are still very definitely present. Although syphilitic rashes vary very much in outward characters, yet in the features just mentioned they have always a basis of close similarity one with another. When mistakes occur they are usually those of insufficient attention. The patient is allowed to decline to shew more than a small part of his surface, instead of being made to strip, or at any rate to expose the whole of his bust. If the latter course be adopted, the symmetry of the rash and its other peculiar features will almost always arrest the attention of the observer. Amongst minor points which occasionally assist may be mentioned the gyrate or ringed form of the patches; and in some cases of syphilitic psoriasis the comparative absence of desquamation.

Secondary eruptions are usually developed in stages. The first stage is one often overlooked, and may be very transitory. In it the eruption is erythematous only and may closely resemble a roseola, and may even be mistaken for German measles. Papules which do not wholly disappear on pressure and are attended by some thickening, soon follow, and with them often occur affections of the pilo-sebaceous system, lichenoid indurations, or small pustules. These stages are often ill-defined, and eruptions of various types are often present together.

The cases which cause most difficulty are those in which syphilis occurs in a patient who is already the subject of some other skin disease. In hospital practice it is very common to see scabies and a syphilitic rash co-existing, and in some of these mixed cases it is most difficult to be certain as to the nature of the eruption. Examination of the mouth and throat and of the genitals will often remove doubt; but, if not, a few sulphur baths will usually prove a successful means of diagnosis. Pityriasis rosea, an eruption now well recognised, so closely resembles a secondary syphilitic rash that it is unsafe for even the most practised observer to make a diagnosis without attention to the history and concomitants. Mistakes in reference to this eruption are frequent, for it occurs most often in young adults—precisely those most likely to be suspected of venereal affections. The suddenness of its onset, its great

abundance, and its comparative sameness of type are all useful in diagnosis, but they must be corroborated by the entire absence of other symptoms.

Next to that of the exanthem itself comes the diagnosis of the *relapses of eruption*, which often occur between the secondary and the tertiary epochs. In these there is rarely any copious outbreak, usually only a few isolated patches. These are most commonly met with in the palms of the hands or soles of the feet, or on the front aspects of the fore-arms or legs. They are almost always dry and attended with peeling of the epidermis. Very frequently there are small sores in the mouth or on the tongue; at the same time a form of acne, chiefly affecting the fore-head, and leaving little pits or scars, is very often seen in this stage. If iritic adhesions be present, or if there be pits in the skin of the face and trunk, left by a former rash, the suspicion is much strengthened. The suppurating and thick-crusted eruption known as Rupia often occurs at this period, but rarely at any great distance of time from those of distinctly secondary type. It is usually symmetrical, and leaves behind it the round and superficial cicatrices so well known as "shilling" scars.

Lastly, we must consider the recognition of the various diseases which come into the category of *tertiary symptoms.* When these occur, it is often many years since the patient has suffered from any other, and it is quite possible that he may appear to be in excellent health. A few of the tertiary symptoms have been so long recognised in relation to their true cause, and are so rarely met with in connexion with any other, that in themselves they almost constitute their own diagnosis, and often also help us to that of more obscure lesions. Periosteal swellings or nodes are the chief of these. To speak generally respecting other forms, we may say that the diagnosis must be founded in part upon the patient's previous history, in part upon any still existing remnants of former disease—such, for instance, as iritic adhesions—and in part upon the peculiarities of the symptoms themselves. As regards the patient's antecedents, I may just remark, by way of caution, that we must not hastily assume that he is syphilitic because he tells us that he has had the venereal disease. A soft chancre with its suppurating bubo, or even an attack of gonorrhœa, although both of them quite innocent as regards constitutional infection, often leave more vivid impressions on the patient's mind than do an indurated sore and its exanthem. Those who are most ready to suspect in themselves a venereal cause, are often those who have never had true syphilis at all. If, however, there is a clear history of a chancre, followed by secondary rash, sore throat, and so forth, then we have obtained facts which, whatever may be the present ailment, may be safely permitted to guide our treatment. The majority of tertiary lesions are by conventional usage regarded rather as surgical than medical, and it would be out of place here to speak in detail of the diagnosis of ulcers, gummatous tumours, and so on. I may briefly remark that the serpiginous form of ulceration, healing in the centre and spreading at the margin, is a feature always to be regarded with

suspicion; and I may repeat that tumours in muscle, which will wholly melt away under the influence of the iodide, are sometimes as hard and as defined as any variety of malignant growth, and have often led to needless operations.

In cases of disease of the nervous system in which syphilis is suspected, an examination of the patient's eyes, throat, tongue, and tibias should never be omitted. The existence of iritic adhesions, of scars of the soft palate, or of periosteal nodes, will often decide the question. The occurrence of nocturnal exacerbations of pain also is always suspicious. If the disease implicate only one nerve-trunk, especially if only one cranial nerve be involved, the suspicion of syphilis becomes very strong. Probably a very large proportion of the cases of paralysis of the third, fourth, fifth, and sixth nerves, when such paralysis affects only one nerve, are due to syphilis, and are curable by specific treatment. In these cases the disease is hardly ever symmetrical, and the paralysis is usually complete. The seventh nerve is occasionally attacked, but not so frequently as the others. The nerves of special sense are not so frequently affected in acquired syphilis as they are in the inherited form. Nevertheless, cases do occasionally occur in which blindness with white atrophy or complete deafness is met with in the subjects of syphilitic taint, and without other assignable cause. In these the loss of function is usually symmetrical, and probably depends upon disease of the cerebral centre rather than on neuroma of the nerve-trunks. I am not aware of any cases in which paralysis of the branches of the eighth pair have been definitely traced to syphilis, but no doubt such occur and might be recognised by due search. Paralysis of single nerve-trunks of any of the spinal plexuses—more especially of those of the brachial plexus—are now and then encountered. It is impossible to exaggerate the importance of headache as a symptom in cases of tertiary syphilis, and especially in those attended by other affections of the nervous system. Headache, if new to the patient, and particularly if severe and nocturnal, should always be allowed to imply the necessity for prompt and efficient specific measures. If not caused by actual meningeal inflammation, headaches may be due to arterial disease, and may be premonitory of thrombosis and paralysis. A few doses of antipyrin and aspirin may be tried, but are not to be trusted unless immediately effectual.

The Diagnosis of Inherited Syphilis rests on somewhat different data. Indeed, the whole course of the disease, when transmitted, presents some remarkable features of difference which I have endeavoured to bring into clear contrast in the appended tabular parallel. (See p. 379.) Some local lesions, not infrequent in those who have inherited the taint, occur with extremest rarity in those who have acquired it, as for instance interstitial keratitis. Others present important modifications of character; thus when periosteal nodes occur in children, they are much more extensive than they usually are in adults. Speaking generally, the so-called "tertiary" symptoms of inherited syphilis, however long the interval of latency may have been, are for the most part

symmetrical. We have seen that those of acquired syphilis are but rarely so.

The early stages observed in the course of inherited disease are for the most part similar to those of the acquired form.

In the infantile period we recognise syphilis by the peculiarity of certain single symptoms; or, more frequently, and with greater certainty, by the peculiar grouping of several different symptoms. First in importance is the rash on the skin. The rashes, as in acquired syphilis, may vary much in their character, but the commonest are the erythematous and the papular. If it be erythema the redness will shew itself in abruptly margined patches, and will be characterised further by its peculiar red or coppery tint, compared by some authors to that of the lean of ham. Sometimes we see instances of dry, scaly rashes in infants, but these are rare. Pustular, vesicular, and bullous rashes are also not infrequently witnessed. Condylomas at the anal orifice are common, though less frequent during the first few months than at later periods. At the same time as the rash, the little patient almost always displays the characteristic sign known as "snuffles," and there is usually inflammation of the mucous membrane of the mouth and sores at its angles. Iritis occurs in a few cases, has similar tendencies to those seen in the acquired form, and is equally under the influence of specific treatment. It occurs also at the same stage, always amongst the secondary symptoms. Inflammation of the deep-seated structures of the eye—of the vitreous, retina, choroid—are as frequent as they are in the adult, and present the same characters. In some cases there is a slight form of diffuse periostitis of the skull-bones, and more rarely inflammation may occur at the junction of the epiphysis and shaft in many long bones.

During the stage of outbreak of the exanthem, which lasts, on the average, from the fourth week to the sixth month, the child becomes fretful, pale, and emaciated; growth is for a time arrested, and the shrivelled face resembles that of an old man. Emaciation is certainly the rule, but it has many marked exceptions, and we often see syphilitic infants who are fat and plump and look remarkably well.

At or about the age of one year, if the child have survived, it is usual for the secondary symptoms to disappear entirely. A period of latency now ensues, during which the child often enjoys very good health. Sometimes relapses occur, and such subjects are especially liable to be affected by condyloma. These relapses scarcely ever involve a return of cutaneous rash. I think that all observers will bear me out in the statement that the characteristic rashes so often seen in syphilitic infants are never witnessed at later periods of life.

At or after the age of puberty the recognition of the existence of inherited syphilis may sometimes be made with great certainty; at other times it is surrounded by difficulties. Our most valuable aids are the evidences of past disease, more especially of the inflammations which may have occurred in infancy. A sunken bridge of the nose caused by the long-continued swelling of the nasal mucous membrane when the bones were

soft, a skin marked by little pits and linear scars especially near the angles of the mouth, the relics of an ulcerating eruption, and protuberant frontal eminences consequent upon infantile periostitis, are amongst the points which go to make up what we recognise as the heredito-syphilitic physiognomy. Added to them we have very valuable aid furnished by the shape of the incisor teeth. In these patients it is very common to find all the incisor teeth dwarfed and malformed. Sometimes the canines are affected also. These teeth are often narrow, rounded, and peg-like; their edges are jagged and notched. Owing to their smallness their sides do not touch, and interspaces are left. It is, however, the upper central incisors which are the most trustworthy for purposes of diagnosis. When the other teeth are affected, these very rarely escape; very often they are malformed when all the others are of fairly good shape. The characteristic malformation of the upper central incisors consists in a dwarfing of the tooth, which is usually both narrow and short, and in the atrophy of its middle lobe. This atrophy leaves a single broad notch (vertical) in the edge of the tooth; and sometimes from this notch a shallow furrow passes upwards on both anterior and posterior surfaces nearly to the gum. This notching is usually symmetrical. It may vary much in degree in different cases; sometimes the teeth diverge, while in others they slant towards each other. Fig. 6 illustrates a good example of the deformity. In any case in which the

FIG. 6. Teeth in inherited syphilis. FIG. 7.

malformation is as marked as in this sketch, no hesitation need be felt in pronouncing the possessor of the teeth to be the subject of inherited syphilis even in the absence of other testimony. I have never yet seen such teeth, excepting in patients of this class. In the majority of cases, however, the condition of the teeth is sufficient only to excite suspicion and not to decide the diagnosis. In a few rare cases only one of the upper central incisors is malformed, the other being of natural shape and size. A good instance of this state of things is shewn in Fig. 7.

In a considerable number of cases of heredito-syphilis the teeth shew no deviation whatever from the normal standard, and in such the diagnosis must be based on other conditions. In addition to the peculiar malformations above described and illustrated, there are others which, although less characteristic, are yet very valuable to a trained observer. They do not, however, admit of description without great risk of misleading the reader. Before leaving the subject of dental malformations I may again point out that it is only in the permanent

set that any peculiarities are observed. The first set are liable to premature decay, but are not malformed.

In addition to the peculiarities of physiognomy and the malformations of the teeth, the diagnosis may be much helped by observing the state of the eyes and of the bones. If there be evidences of past iritis, or if there be marginal clouds in the substance of the corneas, the results of past keratitis, or especially if the corneas be now attacked by this peculiar inflammation in its acute stage, very valuable evidence will have been obtained. The phenomena of syphilitic keratitis in its acute stage are peculiar and easily recognised. Both eyes are usually affected at the same time. The corneal tissue becomes very extensively opaque by the effusion of lymph into its substance; its tint may vary from that of ground glass to a red salmon colour. There are no ulcers in its surface. A zone of ciliary congestion is usually well marked. Whilst the disease is at its height the patient is often for several months practically blind. The intolerance of light is usually considerable. After the inflammation has passed away the cornea usually clears in a most remarkable manner, but it rarely regains such perfect transparency that the experienced observer cannot detect traces of what has taken place. These traces consist in a somewhat dusky and thin sclerotic in the ciliary region, and in the presence of slight clouds here and there in the corneal substance, there being no scars in its surface. The difference between these interstitial clouds and ordinary leucomas is easily observed.

In a few cases the existence of nodes on various long bones may help us to a diagnosis; in others we may obtain aid from finding that the patient has become deaf without otorrhœa, or that he is partially blind from choroiditis. What are known as Parrot's bosses are low elevations on the parietal eminences caused by infantile periostitis.

With regard to the general arrest of development [infantilism] in heredito-syphilis, I may remark that it is a very untrustworthy indication. In a few cases this taint dwarfs the whole body in a most remarkable manner, but in most cases no retardation of general growth is observable. A pale complexion is almost always met with. It is exceedingly rare to meet with a good florid complexion in a young adult who is the subject of this taint. We do, however, every now and then see a physiognomy which neither in shape of features nor in colour of cheeks and lips furnishes the slightest clue. I have met with arrest of sexual development in one or two instances. In one of these, a young woman who was under the care of Dr. Hughlings Jackson in the London Hospital, there was such an entire absence of all sexual characteristics, that I could not but suspect that the ovaries had been destroyed by syphilitic inflammation in early life.

Contrasted Parallel between the Course of Symptoms in Acquired and Inherited Syphilis

I have endeavoured in the following tabular statement to compare as clearly as I can the resemblances and differences in the course of symptoms

when arising from acquired or from inherited taint. To some of these I have already incidentally alluded, and respecting the others the statements in the table will, I trust, explain themselves :—

ACQUIRED DISEASE

Primary Stage.— Local or stage of inoculation. The sore, which may have been present almost from the first, does not assume characteristic features until the end of a month. It may remain for a fortnight to six months.	An ulcer (chancre) usually with indurated base. Indurated lymphatic glands. Induration is to be regarded as the earliest proof of infective inoculation, but it is not infrequently absent throughout.
Secondary Stage.—Systemic or exanthem stage. Usually commences within six weeks or two months of the inoculation, and if not treated, may last from three to six months or a year. Essentially transitory, and will usually disappear without treatment.	Febrile disturbance, malaise and muscular pains. Slight engorgement of lymphatic glands in many parts. A symmetrical and usually copious eruption on the skin, and often on exposed mucous surfaces. Symmetrical ulcers on tonsils. Iritis, retinitis, etc. ; usually symmetrical. Loss of hair, flesh, and strength. This stage may be either exceedingly slight or very severe. Its severity appears to bear proportion to the degree of induration of the preceding chancre. It is often noticed that the rash comes out in successive crops. The rash may also vary very widely as to its character, roseolous, scaly, papular, pustular, ecthymatous, etc., being modified probably by peculiarity—first, in the source of contagion ; secondly, in the idiosyncrasy of the recipient. The whole of the arterial and capillary system may suffer.
Intermediate Stage.—Stage of latency or of relapses. This stage may be said to commence at from a year to a year and a half after the contagion, and to extend over a period which may vary from three to five, ten, or even twenty years. It passes insensibly into the tertiary stage.	The patient may be either wholly free from symptoms and in good health, or he may remain pale and rather feeble, and liable from time to time to slight returns of eruption on the skin, sores on the mucous membranes, condylomas, etc. The arterial system is still liable to be affected, and various forms of paralysis may result. He is protected as regards fresh contagion, and should he beget children they are very likely to suffer. The relapses during this stage are usually easy to distinguish from true secondary symptoms. There is little or no febrile disturbance, the rash is not copious, and often not symmetrical. Acute iritis, retinitis, etc., very rarely occur ; that is, they do not occur for the first time, though they may in the form of relapses.

Tertiary Stage, or stage of sequels.

This stage commences at from four to ten or to twenty years after the contagion, and extends indefinitely, occasionally to the end of life.

All the symptoms in this stage occur, as a rule, without bilateral symmetry. They are sometimes multiple, but not infrequently single. They consist of chronic inflammations of deep tissues, or of the deeper layers of superficial ones, for example—inflammations of periosteum and bone resulting in nodes; of cellular tissue, tendon, or muscle, resulting in gummas; ulcerative destruction of the palate and pharynx; serpiginous ulcerations of the skin; inflammations of nerves, or even of cerebrospinal centres, inducing various forms of paralysis; deposits in liver, lungs, etc. Diseases of the arterial system are now less common. Probably little or no liability to transmit the disease to offspring. Protection against a new contagion incomplete. All the inflammations in this stage are remarkably under the influence of treatment by iodide of potassium, but tend to relapse. Mercury is useful in many, but not in all. Unless treated, all of them tend to progression and permanent disorganisation of the part attacked, none of them to spontaneous recovery.

Inherited Disease

Primary Stage.

The infants usually remain without symptoms for from one week to three months.

This stage has been passed through by one or both of the sufferer's parents within from a few months to several years before the infant's birth. The infant never exhibits any trace of a primary sore and is usually free from all symptoms at the time of birth.

Secondary Stage.—Systemic or exanthem stage.

From the age of two to four weeks to the end of the first year.

This stage is essentially transitory, and, if the child survives, will usually disappear without treatment.

Inflammation of nasal mucous membrane causing "snuffles."

A symmetrical and usually copious eruption on the skin. Wasting; fretfulness; a peculiar odour; a withered, senile aspect; inflammation of the mouth, and condylomas at anus; iritis, usually symmetrical; arachnitis and slight effusion; disease of liver; nodes. Periostitis of the skull-bones frequently occurs symmetrically. The eruptions which occur differ from those of acquired disease, chiefly in being more moist, and in preferring the thighs and genitals. These differences may in part be due to peculiarities in the skin of young infants, and to the constant irritation from urine to which the nates are liable. Dry scaly rashes are rare. Iritis is much less frequent than in the adult, but just as well characterised when it does occur.

In infants this stage often proves fatal.

Intermediate Stage.—Stage of latency.

This stage extends from the end of the first year or eighteen months to the second dentition, the time of puberty, or even very much later.

The patient will probably be wholly free from active symptoms, but will shew various indications of his diathesis in pallor of skin, sunken nose, protuberant forehead, and premature loss of the upper incisor teeth. Sometimes there will be a remarkable retardation of growth and general development. When second dentition occurs, the central upper incisors may very probably be malformed. Unlike what happens during this stage in acquired syphilis, we scarcely ever observe any tendency to relapses of the secondary symptoms. Now and then we see condylomas at the anus returning during the first five years, but the rash of infantile syphilis having once disappeared, scarcely ever relapses. A certain degree of nasal obstruction sometimes persists, but not often.

Tertiary Stage, or stage of sequels.

This stage may commence with the second dentition, at the time of puberty, or not till much later. Its duration is quite indefinite, and its symptoms very peculiar.

Most of its symptoms are symmetrical :—

Keratitis (interstitial) ; kerato - iritis ; periosteal nodes ; deafness (not infrequent) ; blindness (rare) ; disease of liver and kidneys ; phagedænic or serpiginous ulcerations of skin ; cellular nodes (rare). Probably not liable to transmit the disease to offspring. Protection against a new contagion incomplete. The symmetry of the symptoms is in marked contrast with what occurs in the true tertiary stage of the acquired disease. The paralysis of single cranial or spinal nerves, so common from acquired syphilis, are seldom met with in the inherited form.

Most of the inflammations tend, unless arrested by treatment, to permanent disorganisation, but one (interstitial keratitis) tends to recovery even without treatment. They are much less easily influenced by specifics than those of the acquired disease. Disease of the arterial system and its consequences, so common in acquired syphilis, are very seldom seen in the subjects of inherited taint.

JONATHAN HUTCHINSON.

INFECTIVE DISEASES OF DOUBTFUL NATURE

MEASLES
GERMAN MEASLES
SCARLET FEVER
CHICKEN-POX
SMALL-POX
TYPHUS FEVER
INFECTIVE CORYZA
WHOOPING-COUGH
MUMPS
GLANDULAR FEVER
RHEUMATIC FEVER

COMMUNICABLE FROM ANIMALS TO MAN

VACCINIA
FOOT-AND-MOUTH DISEASE
HYDROPHOBIA

CO-EXISTENCE OF INFECTIOUS DISEASES

MEASLES

SYNONYMS.—*Morbilli*; Fr. *Rougeole*; Ger. *Masern.*

By DAWSON WILLIAMS, M.D., F.R.C.P.

MEASLES is a specific, infectious, eruptive fever, characterised by coryza and catarrh of the upper part of the respiratory tract, and by a peculiar blotchy eruption on the skin.

Statistics.—The liability of all races of mankind to measles appears to be equally great. No age, however advanced, affords protection, and infants have been born with the rash. It is true that a far larger number of cases occurs among children than among adults, but this is because in civilised countries few individuals escape infection during childhood.

In Great Britain about 60 per cent of the deaths from measles occur in children under two years of age, about 90 per cent among those under five, and about 98 per cent among those under ten. The mortality under six months of age is comparatively small, and it is probable that about half the individuals who die of this disease are children between the ages of six months and two years. Persons appear to be attacked with equal frequency at all ages in isolated communities—such as those of Fiji and of the Faroe Islands—into which the infection of measles is introduced for the first time or after a long interval.

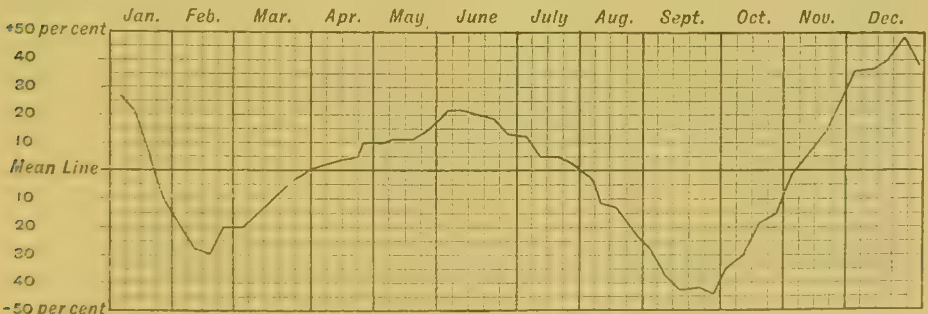

Chart 4.—The mean line represents an average weekly number of 34 deaths.

Fifty years 1841-90.
From the *Annual Summary* (London and other great towns), 1890, issued by the Registrar-General.

The statistics of the Registrar-General shew that measles in England and Wales attains a maximum at two periods in each year—in June and

December; but there are also years of epidemic prevalence, when the mortality reaches an exceptionally high level. Dr. Whitelegge states that in English towns the interval between these epidemic outbursts is usually about two years, but that it is occasionally six months more or six months less—due, as he suggests, to the fact that the seasonal curve shews two maxima. He believes, also, that there is distinct evidence of an epidemic wave of longer period, recurring at intervals of about ten years, when a very high mortality is produced. He points out also that in populous places the fatality of measles may become gradually greater through a series of epidemics, until a rate double or treble that of the ordinary seasonal maximum is reached.

The case-mortality of measles varies much in different epidemics, and in relation to the age, previous state of health, and sanitary surroundings of the patient. The mortality from this cause among children in foundling institutions may reach an enormous proportion: thus in the Hospice des Enfants Assistés in Paris the deaths reached an annual average of 44 per cent in the four years 1882 to 1885 (7).

While it is true that there is evidence that the severity of the disease itself varies in different epidemics, a much more important factor appears to be the goodness or badness of the hygienic conditions under which the children are placed. Chief among the causes of a high mortality are overcrowding and insufficient ventilation, which favour respiratory complications, especially bronchopneumonia. The mortality in the Paris institution already mentioned has been reduced at least one-half by systematic isolation not only of the children suffering from measles, but also of children suffering from measles complicated by bronchopneumonia from other children with measles but not presenting this complication. In an epidemic of a mild type the mortality among children treated at home may be almost nil; though the deterioration of health due to the disease, and in particular the special liability to the development of fatal tuberculosis which it produces, exercise some influence in increasing the death-rate of a district. The mortality of persons attacked with measles varies greatly with age. It is highest between the ages of six months and two years, and falls rapidly after the fourth year. Henoch had among hospital cases a mortality of 55·5 per cent among 133 children under two years of age, and of 9·5 per cent among 161 children over two years old. Gannelon's statistics from the Hospice des Enfants Assistés are as follows:—

0–6 months,	23·68 per cent.	3–4 years,	13·66 per cent.
6–12 „	57·77 „	4–5 „	6·20 „
1–2 years,	53·94 „	5–10 „	2·4 „
2–3 „	27·73 „	10–21 „	0·0 „

Embden, during an epidemic at Heidelberg, had among cases treated at home a mortality of 14 per cent in children one year old or under, 7·5 per cent in children from one year old to four, and 2·2 per cent from four years old to thirteen. The main cause of the high mortality

in hospitals among children under four years old is bronchopneumonia; though the occurrence of membranous pharyngitis or laryngitis is also responsible for a large number of deaths (*vide* also vol. i. p. 64).

Pathology.—The mode in which the infection of measles is contracted is in most cases personal intercourse. The infection is perhaps greatest during the earliest stage. It is present at the onset of the prodromal symptoms, possibly even a little earlier, and persists down to the time when the rash fades. Thereafter it declines rapidly. Though infection may be derived—especially, perhaps, if desquamation be well marked—from a person who has recovered sufficiently to resume his ordinary occupation, it is rarely that infection can be traced to a convalescent later than three weeks after the commencement of his attack; though infection may persist longer in complicated cases. On the other hand, it is probably as great on the first day of the prodromal symptoms, even though these be slight, as at any subsequent date. Though not infrequently conveyed by clothes, it is seldom retained long by fomites or utensils. Though it is highly probable that measles is due to a specific micro-organism its nature is as yet unknown. The important part played by infective organisms in the complications, which are in the main responsible for the mortality of measles, will be considered subsequently.

The eruption is produced by congestion and leucocytic infiltration. The infiltration is greatest about the vessels, the sebaceous glands, and the sweat-glands. When the congestion is sufficiently intense, small hæmorrhages may occur into the derma or subcutaneous tissues. There is also some infiltration into the superficial papillary layer. Localised colloid degeneration of the cells may ensue, producing the false appearance of a vesicle crowning a papule produced by the intense congestion about the centre of degeneration.

It is difficult to distinguish the visceral lesions due directly to the infection of measles from those produced by secondary infections. The catarrh of the mucous membrane of the eyes, nose, mouth, pharynx, larynx, and bronchi favours the development of secondary processes due to infection—in the mouth, nose, and larynx by pyogenetic organisms, in the lungs by the various organisms associated with pneumonia, and in the larynx by "diphtheria." The bronchopneumonia does not differ from that not secondary to measles, except perhaps by the greater rapidity with which it develops, and a greater tendency to the formation of pus. Cornil and Babes have described a special form of pneumonia the primary lesion of which appears to be an inflammation of the lymphatics and interalveolar connective tissue; fibrinous exudation occurs at first in these situations, and invades the alveoli later. On account of this peculiar distribution it is held that this form of pneumonia is due to the primary infection of measles. The exudation it produces undergoes granular and then fatty degeneration, leading to the formation of caseous areas which simulate tuberculosis. Tuberculous disease of the lungs is found in a large proportion of children, over five years of age, who die some little time—weeks or months—after the onset of measles. In some of these

cases there is true miliary tuberculosis, which may invade not only the lungs but also the spleen, meninges, and other organs; in others there is tuberculous caseation of the bronchial glands, or caseous areas in the lung, though these are often masked by attendant bronchopneumonia. Inflammatory engorgement of the bronchial lymphatic glands is the rule, and some simple chronic enlargement may persist, though tuberculous adenitis is probably the more common sequel.

Incubation.—The interval between exposure to infection and the onset of the prodromal symptoms is usually ten days, but may be as short as five or perhaps four days. On the other hand, it may be as long as fourteen days, in which case the rash would not appear until the seventeenth, eighteenth, or even the nineteenth day after infection. Though the period of about fourteen days from exposure to the appearance of the rash is that met with in the vast majority of cases, it is important to recognise that it may be four or five days longer, since such exceptional cases must be taken into account in estimating the period for which a susceptible person who has been exposed to infection should be isolated from other persons who have not had the disease. An interval of a full fortnight must be allowed; and at the end of that time the person must be free from fever, catarrh, and photophobia before it can be said that he has escaped infection.

Symptoms.—*Prodromal Stage.*—From eight to ten days after exposure to infection the patient begins to suffer from catarrh of the mucous membranes of the eyes, nose, pharynx, and larynx. The temperature is raised (102° to 104° F.), cough is troublesome, but, beyond a little scattered sibilus, examination of the chest reveals no physical signs. The face is puffy and pale, or a little dusky. The eyes water, the sclerotic is injected, and the palpebral conjunctiva red and swollen; there is some photophobia, it may be much. A thin, watery fluid, discharged from the nose, irritates the upper lip; the voice and cough are hoarse; the tongue is covered by a white fur, its edges are red, and the papillæ enlarged. The mucous membrane of the mouth and pharynx is red, œdematous, and loses its polish. In a large proportion of cases during the prodromal stage, and usually first on the second day, certain characteristic spots may be observed on the buccal mucous membrane. They should be looked for on the cheeks opposite the molar teeth, and consist of minute opalescent spots, white with a faint bluish tinge, with a red or pink areola. Their characters can only be recognised in a white light, diffused daylight being best, and, when found, appear, according to Bing, the latest writer on the subject, to be pathognomonic. They were first noticed by Flindt at Samsoë in Denmark, but the credit of drawing general attention to their diagnostic importance belongs to Koplik of New York, and they are often spoken of as Koplik's spots or sign. The areola around each spot gradually enlarges, until by a coalescence the mucous membrane becomes generally red, closely-set with the minute opalescent spots. The opalescence appears to be due to local collections of œdematous epithelial cells, and the spots usually disappear soon after

the time of the appearance of the eruption. Opinions differ as to the constancy of this sign, but Holt, in a series of 187 cases in one epidemic, found the spots in 169 cases, doubtfully present in 10, and absent in 8 only. In 54 patients the sign was noticed one day before the rash, in 25 two days before, in 4 three days before, and in 2 five days before. In 2 cases they were not seen until after the skin eruption, and in 78 cases fever, rash, and Koplik's spots were all present at the first observation. In one case only were the spots seen in a case in which no eruption was observed, but this patient had been exposed to eruption and had prolonged fever. In only one case were the spots seen before any elevation of temperature. The aspect of the child in the prodromal stage, if not entirely characteristic, is at least extremely suggestive. On the second day the temperature is higher, the secretion from the nose and naso-pharynx is muco-purulent, and the glands, especially those behind and beneath the lower jaw, are enlarged and tender. An eruption of closely-set red points may be visible on the palate and the buccal mucous membrane. The child as a rule is extremely irritable, owing in great part to the distress caused by the photophobia and by thirst. Shivering fits, or, in young children, convulsions, may occur during the prodromal stage; these, however, are generally slight and of short duration. In some epidemics the patient during the prodromal stage remains in a dull, somnolent state. During this period there may be marked symptoms of laryngitis, or, especially in quite young children, attacks of laryngismus. In some epidemics epistaxis has been observed in a large proportion of cases, occasionally to a serious extent.

Eruptive Stage.—The eruption appears on or about the fourth day, often in the night between the third and fourth days. It is noticed first on the forehead, at the edge of the hairy scalp or behind the ears; and a little later on the cheeks, chin, and neck: after some hours it spreads downwards, reaching in succession the trunk, arms, and lower limbs. It begins to decline in about twenty-four hours, so that it may be fading on the face while yet it has not reached its full intensity on the lower limbs. Occasionally there are distinct short intervals between the appearance of the rash on the face, the trunk, and the limbs. In other cases, after coming out well on the face, it fades rapidly and does not reach the trunk. This rapid disappearance of the rash is sometimes observed in very mild cases; sometimes it marks the onset of serious visceral complications, as the general condition of the patient, the temperature, and the physical signs will indicate. The rash, especially that on the face, is at first a diffuse redness, or consists of closely-set red points; but in a few hours small, round, red spots, which give to the finger the sensation of very low flat papules, form in the affected parts. As they enlarge they form patches, often crescentic in form, with a scalloped edge, and assume a dusky red or mulberry colour. When they reach this stage the colour of the patches is not discharged by pressure, and small ecchymoses frequently appear. While the rash is coming out the catarrhal symptoms persist, or are somewhat aggravated;

the laryngeal symptoms in particular may become more marked, owing to extensive catarrh of the mucous membrane, which may cause even a slight reddening of the vocal cords themselves.

The eruption may be irregular in character, intensity, and distribution. An unusual amount of congestion may, by throwing up the hair-bulbs, give rise to a papular appearance, which, if the rash be scanty, may resemble the early stage of varioloid. The rash at its first appearance may be so intense and confluent as to cause an almost uniform reddening of the face, neck, and chest, so as to suggest scarlet fever; but, even if the reddened areas cannot be made out to have a well-defined scalloped edge, the nature of the eruption will be evident after a few hours. In rickety children and in warm weather the true rash is often preceded by sudamina. In children infested by fleas or lice the general tint of the rash may be deepened by very numerous petechiæ or by "marbling." Ecchymoses, especially on the back and thighs, are frequently produced in cachectic children; in whom also the rash is commonly discrete and pale.

Physical signs of bronchitis are seldom absent during this stage. Sibilant rhonchi may be heard in all parts of the chest, especially in the interscapular region, and give way after a short time to moist râles. The expectoration, seldom observed in very young children, is at first clear and stringy; later it becomes purulent and nummular. In both stages it is remarkably viscous and tenacious. The child continues to be extremely thirsty, but refuses food. Diarrhœa of foul-smelling slimy stools very commonly occurs during the eruptive stage, either at the onset of the rash or as it fades. The child is restless and peevish by night, but often sleeps much in the day.

As a rule the eruptive stage lasts three or four days, but may continue for six.

Convalescent Stage.—After an uncomplicated attack convalescence is as a rule rapid. As the rash fades thirst diminishes, the nasal discharge decreases, sleep becomes natural, and appetite returns. Cough and some photophobia remain for a few days more; but the signs of bronchitis clear up rapidly, and at the end of ten days or a fortnight from the onset of the prodromal symptoms the child may appear to be quite well. A little fine branny desquamation may generally be observed, especially about the face, neck, and waist; occasionally it is very extensive and detached in flakes, especially if there has been some miliary eruption.

Departures from the usual Type.—*Mild Forms.*—The symptoms of the prodromal period may be so slight as to pass quite unobserved. Occasionally the period is prolonged to six or eight days. The disease sometimes appears to abort early in the eruptive stage, and convalescence begins about the second day of that period. Occasionally, during an epidemic of measles, cases characterised by fever, coryza, bronchitis, and gastric derangements, but without any rash, are met with; as these patients are found to be immune on subsequent exposure to the infection

of measles a possibility of the occurrence of measles without rash must be admitted.

Malignant Forms.—Though measles, if uncomplicated, is, as a rule, benign, it may be a most severe disease, owing either to the intensity of the infection or to the cachectic or unprotected condition of the individual attacked. Several forms of malignant measles are met with, and must be distinguished from those cases which become severe owing to complications.

In cases of the *typhoid* type there is said to be retrocession of the eruption; that is to say, the rash either does not come out well, or its evolution is suddenly stopped. Simultaneously the pulse rises to 130 or 140, the respirations to 60 or 80, the temperature to 104° or 105° F.; the tongue becomes dry, the lips cracked, the skin burning, and the amount of urine is much diminished. The profound nervous disturbance present, which must be attributed to toxæmia, is evidenced either by extreme depression and somnolence or by excitement—severe convulsions in children, and delirium in the adult. The state of excitement may pass off as rapidly as it developed, or the patient may sink into a comatose state, which rapidly ends fatally. Between these two extremes every degree of severity may be observed. In some epidemics, especially in schools and barracks, cases occur in which the patient, at or about the time of the outbreak of the rash, becomes cyanosed and suffers from severe dyspnœa. Cough is frequent, and the expectoration, if present, is frothy. There are at first no physical signs to account for this condition; but after a few hours fine mucous râles are heard everywhere in the chest, and the patient succumbs to what is commonly called capillary bronchitis. These cases are probably examples of the severest form of the special type of pneumonia described by Cornil and Babes. In the adult death may be very sudden, and due to syncope. The eruption is scanty, or fades at the onset of the dyspnœa. To this form the term *suffocative* has been applied. In some cases, presenting symptoms of the typhoid form, the rash assumes a livid colour; and hæmorrhages, more or less extensive, take place into the skin. Epistaxis and hæmorrhage from the mouth and bowels may occur. To this form, which occurs in cachectic subjects, the term *hæmorrhagic measles* properly belongs. The extremely severe examples of this form described by the older writers as "black measles" are now seldom or never met with; and as Fagge observes, "One is almost inclined to suspect them of having mistaken cases of hæmorrhagic small-pox for this disease."

The term *secondary measles* is applied to attacks occurring in persons whose health has been enfeebled by a recent attack of typhoid fever or diphtheria, or by tuberculosis, or other general malady producing cachexia. In such persons the disease may run a mild course, but on the other hand it may be of exceptional severity. The prodromal symptoms are not well marked; the eruption is scanty and dusky, or purpuric; the temperature is high and continuous; vomiting and

diarrhœa are common, and in young children bronchopneumonia develops.

Relapse.—It has sometimes been asserted that relapse is of common occurrence in measles, but it seems clear that a true relapse is a very rare event. Some of the cases quoted as examples of relapse are really instances of irregular development of the rash; others rest, apparently, upon an error of diagnosis—the first or the second eruption being in reality that of German measles.

Temperature.—The ordinary temperature curve of measles shews a double summit. The temperature rises rapidly at the onset of the prodromal symptoms, reaching a first maximum of 102° to 104° F. within the first twenty-four hours; for the rest of the prodromal stage it is at a lower level, with evening exacerbations and morning remissions, which may even reach the normal. The lowest point is touched on the morning of the second or third day. The temperature then mounts until the appearance of the rash, when it attains its second maximum, which is generally higher than the first, and may be as high as 105° to 106° F. It does not remain long at the maximum, and usually falls rapidly on the third day of the rash, reaching the normal standard probably on the morning of the fourth day. The fall to normal may be delayed for one or two days: it may be so rapid as to constitute a true crisis, which may be accompanied by profuse sweating, and even by collapse. In other cases the fall is much more gradual, and may extend over three or four days of gradual descent. The curve is much modified if the patient be already suffering from some chronic febrile disorder, or by the onset of complications. In the former cases it is still frequently possible to detect the double maximum; in the latter the fall, after the eruption has come out, is replaced by an elevated temperature, due to bronchopneumonia or to the particular complication under which the patient labours. Sometimes the rapid rise at the onset of the prodromal symptoms cannot be detected, and the curve mounts, with morning remissions, to a single maximum on the first day of the eruption.

Pulse.—The pulse increases in rapidity from the onset of symptoms until the eruption appears, when, in uncomplicated cases, it begins to fall. In uncomplicated cases it seldom exceeds 120 in children and 90 in adults.

Complications.—*Laryngitis.*—Some degree of catarrhal laryngitis ought, perhaps, to be considered rather as a symptom than a complication of measles. It usually decreases soon after the rash appears. In other cases the symptoms increase in severity; voice and cough become first hoarse and then toneless, and movements of or pressure on the larynx excite pain. The expectoration becomes blood-stained. Necrosis of the cartilages may ensue, or œdema glottidis. Such an event is rare; but membranous laryngitis, especially in schools and asylums, is a not infrequent and very fatal complication. It may come on either during the eruptive stage or as late as the second week. In some cases it is due to true diphtheria; in others, perhaps the majority, to infection with pyogenetic cocci. The symptoms—which need not be described here—

are practically identical; but it may be observed that the membrane produced by pyogenetic cocci is as a rule more diffluent or friable than that produced by true diphtheria. The false membrane may invade the fauces and tonsils. The onset of symptoms is commonly more insidious than in primary diphtheria; attacks of dyspnœa are less frequent, and there is less warning of the approach of asphyxia. The results of tracheotomy are extremely bad, and even when some temporary improvement takes place the wound itself is very apt to become the starting-point of phlegmonous inflammation.

Bronchial catarrh, be it more or less, must be considered one of the ordinary symptoms of measles; but the smaller bronchi and the pulmonary tissue are liable to become invaded at any stage of the disease. Reference has already been made to those acute cases, called suffocative, in which the lungs become invaded in the prodromal stage; but, short of these, cases occur to which the term "congestion of the lungs" is commonly applied. The respiration is hurried, there is slight cyanosis, the pulse is rapid and soft, and everywhere over the chest small moist crepitations are heard; the breath-sounds, however, are not bronchial, there is no true fine crepitation, and resonance is not deficient. The cases resemble "capillary bronchitis," but differ from it, inasmuch as all the symptoms and physical signs diminish rapidly at the time the rash appears or soon afterwards. In a few cases only does pneumonia appear. In a small number the symptoms described persist throughout the stage of eruption, and until the period when convalescence ought to begin. Such an occurrence is very suggestive of the lighting up of tuberculosis.

Bronchopneumonia, the most fatal complication of measles, first becomes evident as a rule during the eruptive stage. It may begin about the time when the eruption comes out, or even earlier; or its onset may be deferred until it is hoped that convalescence is about to commence. The symptoms do not differ from those of primary bronchopneumonia; but it should be borne in mind that in a child suffering from measles the lesion is more apt to be progressive. This bronchopneumonia is to be attributed to a secondary infection. The catarrh determined by the primary infection of measles appears to favour the growth of certain pathogenetic organisms, chief among which are the *Pneumococcus*, the *Streptococcus pyogenes*, and the *Staphylococcus pyogenes aureus*. All of these microbes may be found in the secretions of the mouth, nose, and larger bronchi, even in health; but they are more frequently present in children suffering from measles. The so-called subacute or chronic pneumonia of measles, which comes on as the eruption subsides, or later when convalescence appears to have begun, is almost invariably a tuberculous process; there are irregular pyrexia with evening exacerbations, persistent cough, and signs of localised pneumonia which do not clear away.

Influenza.—Bacteriological investigations tend to make it probable that measles is not infrequently complicated by true influenza, and the gravity of the illness thereby seriously increased.

Stomatitis.—Some catarrh of the mucous membrane of the mouth is an almost invariable accompaniment of measles. It comes on during the prodromal stage, and passes away with the eruption. It is of importance, chiefly, because it paves the way for secondary infections; the mucous membrane becoming the seat of diphtheria, ulceration, or aphthæ. Ulcerative stomatitis attacks particularly the sulcus between the lips and the gums; but it may be met with on the cheeks opposite the crowns of the teeth. Small, rounded white patches first form, and the necrosed epithelium becomes detached, leaving an ulcer. The destruction of tissue may extend, and by confluence form large elongated ulcers with sharp edges and a purulent or sloughy surface; they may extend to the outer border of the lips, and are then very liable to cause painful cracks and to bleed. The *Staphylococcus aureus* has been found in such cases in almost pure culture. The ulcerations tend to heal as the fever subsides, and are chiefly of importance because the pain they produce tends to make the child refuse food. If neglected, however, they may persist in a chronic or subacute form for weeks or months.

Diarrhœa.—Looseness of the bowels during the prodromal stage is the rule, and diarrhœa of foul, glairy, or watery stools may be troublesome about the time the eruption appears. Occasionally the diarrhœa is very copious, and the child passes into a condition of collapse; in such cases the rash is ill-developed or fades, and the case may be mistaken for severe summer diarrhœa. Diarrhœa of a dysenteric character, due apparently to diffuse catarrhal colitis, sometimes occurs, and is very apt to continue as a chronic condition for weeks or months.

Vulvitis.—Inflammation of the vulva with muco-purulent discharge is a frequent complication of measles, and may persist for weeks or months especially in strumous children. The inflammation may go on to ulceration, attended by much pain and swelling of the parts, and smarting on micturition. Occasionally the process becomes exceedingly acute, and leads to brawny induration, and even to gangrene (noma).

Otitis.—Eustachian inflammation is a common complication, and is particularly apt to occur in the subjects of chronic granular pharyngitis and adenoid vegetations. Closure of the tube may be revealed by deafness and tinnitus; but in other cases the symptoms are latent, and the only indications that the inflammation has reached the middle ear are some increase of restlessness, grinding of the teeth, sudden cries, and perhaps delirium. These symptoms, which are commonly attended by a sharp rise of temperature, should lead to a careful examination of the ear. Puncture of the tympanum may give immediate relief. If untreated, convulsions may ensue, or the child may sink into a state of torpor from which it becomes quickly aroused as a purulent discharge from the ear indicates that the tympanum has ruptured spontaneously. Before this happens, however, the mastoid cells may have become infected, or meningitis or thrombosis have been produced. The discharge is foul and very irritating, so that, unless special precautions be taken, excoriation of the external auricle rapidly follows.

Conjunctivitis.—*Staphylococcus aureus* and *Streptococci* are the micro-organisms most often present in the secretions of the conjunctival catarrh constantly observed in the acute stage of measles. The inflammation may be very intense, causing great swelling of the lids, and giving origin to a copious sero-purulent discharge. This condition is observed most often in strumous children, and in them phlyctenular ulceration or diffuse keratitis may occur. Occasionally the globe is destroyed by suppuration and rupture.

Gangrene, Noma.—In cachectic children inflammation of some one of the mucous surfaces so commonly involved in measles may take on a peculiar spreading and intense character. This serious complication commonly arises after the subsidence of the eruption, and may with great rapidity produce extensive gangrene and sloughing. This may occur in the mouth (noma, *vide* "Diseases of the Mouth," vol. iii.), vulva, throat, larynx, or ear. It seems to be due to a secondary infection, and is apparently very much less common since the hygienic condition of hospitals, schools, and the dwellings of the poor has been improved. Gangrene of the lung has been occasionally observed.

Renal Disease.—Albuminuria is occasionally observed, chiefly in adults, about the time of the onset of the rash, with which it commonly disappears. It is believed to be due to a temporary congestion, and nephritis is undoubtedly a very rare complication of measles. Chronic albuminuria, with anasarca, has been described as a late sequel of measles, but, to say the least, the connexion is not well established.

Serous Effusions.—Ascites, due apparently to subacute simple peritonitis, occasionally occurs as a late complication of measles. It appears to have been chiefly observed in girls. The fluid is eventually absorbed, but may remain for several weeks in sufficient quantity to cause considerable distension of the abdomen. Anasarca is sometimes observed, even though the urine remains free from albumin. Its cause is not explained.

Affections of the Heart.—In a few instances endocarditis has been observed during measles, and pericarditis still more rarely. It is probable that the latter, if not the former also, may be secondary to broncho-pneumonia.

The number of cases in which any permanent disorder of the *nervous system* is produced by measles is small. In spite of the enormous number of children who recover annually from measles, instances of nervous disorders arising in connexion with the disease are rare.

Mental Disorder.—A few cases are on record in which the patient, after the fever, remained in a dull, apathetic state. In some there is complete dementia, from which recovery may take place suddenly, as in a case recorded by Casson.

Chorea.—Measles is not generally recognised as one of the common antecedents of chorea; but among the 439 cases of chorea analysed by Sir Stephen Mackenzie, for the Collective Investigation Committee, there were thirty-two in which measles was the sole antecedent illness;

and in seventeen others measles, associated with anæmia, was the sole antecedent illness. On the other hand, measles coming on during chorea generally leads to the diminution of the movements.

Tetany.—In young children, especially in those who have convulsions at the onset, tetany may be observed during the disease, and may persist for some time afterwards.

Hemiplegia.—In 120 cases of hemiplegia in children Prof. Osler found four after measles; in eighty cases Sir W. Gowers found seven after measles. The hemiplegia may come on during the height of the disease or during convalescence. In most of the recorded cases it has been first noticed after a fit or a series of fits; and in some instances the spasmodic affection has been limited to the side subsequently found to be paralysed. As is the case with hemiplegia coming on during other acute infectious diseases, aphasia exists in a very considerable proportion of the cases. The occurrence of hemiplegia during the acute stage appears to add to the gravity of the prognosis. If the patient recover from the attack of measles very great improvement may take place in the paralysis, though, apparently, not complete recovery. Schwartz has recorded a case of aphasia and paralysis of the extensors of the upper extremity in which both the power of speech and the movement of the arm were completely regained. In the majority of cases of hemiplegia the paralysis persists, and becomes in time associated with arrest of development, of one or both limbs, rigidity, and exaggerated deep reflexes. The pathology of these cases is not very clear; they have been attributed to encephalitis followed by sclerosis, or to localised meningitis.

Muscular Atrophy.—A few cases of limited muscular atrophy, resembling infantile paralysis, are on record as a sequel of measles. They are so few that were it not that similar lesions occur after other acute specific diseases the relation might be regarded as one of mere coincidence. Their pathology is very obscure; Dr. Ormerod, who has recorded a series of cases in one family, rejects the view that they are due to acute anterior poliomyelitis, and appears disposed to associate them with the progressive muscular atrophy of youth.

"*Ascending Paralysis.*"—A rare complication of measles is a form of paralysis which closely resembles in its clinical features that observed after diphtheria. The suspicion that the paralysis is really secondary to latent diphtheria may perhaps have led to some of the cases not being recorded. Barthez and Sanné mention eight cases in which there could be no suspicion of diphtheria. The symptoms in these cases were those of paresis rather than paralysis of the soft palate, the pharynx, the tongue, and of the muscles of the neck; in four cases they appeared during the earliest days of the disease, and in the four others three weeks after. All the patients recovered in from three to twenty days. On the other hand, cases of this nature may terminate in death. The analogy of diphtheria, taken together with the complete recovery which appears to be the rule, lends support to the hypothesis

that the lesion in these cases is multiple neuritis. Paraplegia appears occasionally during measles; the reflexes are lost rapidly, the electrical reactions of the muscles are much modified, the patient complains of formication and cramps, and there may be retention of urine and incontinence of fæces. Recovery in from one to six weeks is the rule; but death has been brought about by respiratory paralysis, due apparently to palsy of the diaphragm. Lop attributes these cases to lesion of the cord due to toxæmia.

Disseminated Myelitis.—Disseminated myelitis may arise during the course of measles. This is proved conclusively by Sir T. Barlow's case, in which death occurred during the acute stage, and a post-mortem examination was made. In this case the nervous complication came on during the early stage of the exanthem, and such would appear to be the rule. It is in the highest degree probable that the primary lesion was disseminated myelitis in certain other patients who presented, during the acute stage of measles, marked disturbance of the nervous system characterised by stupor, widespread muscular paralysis and loss of control over the sphincters, and who, after recovery from the acute illness, remained permanently affected by symptoms resembling disseminated sclerosis. In one case which I have recorded, in the *Medico-Chirurgical Transactions*, the child was seized with convulsions on the fourth day of an ordinary attack of measles; four weeks later she was in a condition of hebetude, had some difficulty in swallowing, and was unable to sit up, though she could move her limbs feebly. Improvement took place very slowly, and, as she regained power, inco-ordination was a marked symptom, along with coarse tremor on movement. Later, tremor aggravated by intention was present in all the limbs, and involved the head; the deep reflexes were exaggerated. Speech was syllabic. Eventually all the symptoms improved very much; but at twelve years of age she was backward in intelligence, slow of speech, clumsy in movement, and there was some rigidity of the muscles of the limbs and exaggeration of the deep reflexes. It seems highly probable that the disseminated myelitis is due to a specific toxæmia; and this view is confirmed by the fact that the changes found in the cord in Sir T. Barlow's case were clearly vascular in origin. This hypothesis is strengthened by the case reported by Dr. Newton Pitt; in a young adult delirium was followed by coma and incontinence of urine and fæces, but complete recovery eventually took place.

Measles and Pregnancy.—A pregnant woman is rarely attacked by measles, but it does not appear that pregnancy confers any immunity. Abortion or premature delivery is apt to occur either during the eruptive stage or at the onset of the prodromal symptoms. Severe hæmorrhage may occur after delivery. Measles very rarely occurs in the lying-in period after delivery. The prognosis of measles in a pregnant woman is good. The chief dangers are—(i.) that bronchopneumonia, if it occur and the uterus be not emptied, may cause great embarrassment of the respiration; (ii.) that, as the systemic infection of measles appears

to dispose to septic processes, the patients may be rather more liable to puerperal septicæmia. On the whole it is desirable to advise a pregnant woman who has not already suffered from measles to avoid contact with infected persons.

Diagnosis.—A well-marked case of measles can hardly be mistaken for anything else. Mild cases may be difficult to distinguish from German measles (*vide* p. 404). The fine red rash which sometimes precedes the true eruption, owing to its resemblance to the rash of scarlet fever, may cause some hesitation. The history of exposure to infection (if it can be obtained), the presence of coryza and photophobia, the milder degree of throat affection, and the observation of Koplik's spots, if present at the time, will probably lead to a correct diagnosis; but in doubtful cases it is wiser to suspend judgment, and to isolate the case as though it were scarlet fever. A discrete eruption, especially if, as is sometimes the case, there be complaint of pain in the back, may cause the case to resemble varioloid; though the converse mistake has probably been more often made. If the character of the eruption be not conclusive, reliance must be placed mainly on the history and the symptoms of catarrh. Acute, widespread dermatitis ("acute eczema") may present considerable resemblance to measles, and herein mistakes have been made even by experienced physicians. Careful examination of all the circumstances of the case will generally prevent error: on close examination the rash will be seen to differ from that of measles, and as a rule areas will be found, most likely about the neck or behind the ears, where the surface is weeping or covered by thin crusts; there will probably be no coryza or photophobia, and the temperature will not be so high as would attend so extensive an eruption were it that of measles. The only safe course in all doubtful cases is to decline to give a positive opinion on the first occasion of seeing the patient. As a rule a few hours' delay will make a decision possible.

The prophylaxis of measles presents special difficulties owing to its extreme infectiousness before the symptoms are characteristic. Personal intercourse, especially in schools, is the main factor in disseminating the disease. The slight importance which the public is disposed to attach to measles creates a great difficulty. Körösi gives statistics from Buda-Pesth which shew a remarkable diminution in the number of cases of measles during the three months which include the autumn holiday, and a rapid increase commencing about a month after the schools resume.

It is only, therefore, by dealing with the early cases that the spread of an epidemic in a school containing many susceptible children can be controlled. Dr. J. Kerr has pointed out that under such conditions two crops of cases may be expected; the infection for the first crop is derived from the first case probably during its catarrhal stage, for the second crop from the children of the first crop, also during the catarrhal stage. The occurrence of the second and larger crop may be prevented by prompt closure of the class or school, or in the higher classes by exclusion of susceptible children. If this system is to

be successful it is necessary that the history of all the children in a class as to measles should be known. The information should be obtained when the child is first admitted to the school and recorded on an index card; if the child suffers from measles during its attendance in the infants' department the fact is entered on the card, which is passed on with it to each higher class. Should a child be noticed to present symptoms of coryza, reference to the card-index will shew whether or not it has had measles; if it has not it is sent home, and watched, and any other children in the class who may be suffering from cold are likewise sent home. If the first case turns out to be measles the class, if it contain a large proportion of susceptible children, should be closed temporarily. A "first crop" of cases will probably occur, but the second or main crop will be prevented. Closure for a period embracing the twelfth day will usually be sufficient. In classes containing a few susceptible children it may be sufficient to exclude them for the period of twelve days only. Much difference of opinion as to the value of compulsory notification exists among medical officers of health. It is argued that the fact that many cases are never seen by medical men must greatly diminish the good results to be expected from notification; and, further, that the want of means to isolate patients, and to keep under observation susceptible children who have been exposed to infection, must prevent the application of any effectual measures by a public health authority. Early knowledge of an epidemic will, however, enable public health authorities to give parents good advice, to which it is possible that they may after a time be disposed to give ear; and also to supply school authorities with the names of houses or localities in which cases have occurred, so that children from these places can be excluded from the schools. Compulsory notification, it must be confessed, has not hitherto been a very successful means of checking epidemics of measles; but this failure may in part, at least, be because it has never yet been enforced over an area sufficiently extensive. It is of little use to apply the Infectious Disease Notification Act in a town if it be not also enforced in the suburbs. Further, if the best results are to be obtained, it will be necessary to insist upon the provisions of the Act requiring notification by householders, which hitherto have been very generally a dead letter.

Treatment.—*The prevention of complications* is the most important part of treatment. Its two main elements are cleanliness and ventilation: but it is advisable to keep the child in bed from the onset of symptoms until desquamation is over, or, if this be not noticeable, for a week or ten days altogether. The danger of exposure to cold has been greatly exaggerated. Vierordt recommends that on warm, sunny, still days the child should be rolled out of doors in its bed, care being taken to guard the eyes from light. The room in which a case of measles is nursed should be thoroughly well ventilated, but great variations in its temperature or exposure of the patient to direct draught should be avoided. In a private house it is a good plan to use two adjoining

rooms—the one by day and the other by night; each room while not in use should be cleaned, dusted with a damp cloth, and the windows left wide open. Dust and smoke should be avoided, as they tend to increase the irritation of the mucous membranes. Dryness of the air not only increases this irritation, but also favours the dissemination of dust and microbes; if necessary, it should be moistened artificially by the steam from a boiling kettle, or by evaporation from an open dish over a spirit lamp. The use of a steam-spray presents the advantage that some aromatic disinfectant may be added from time to time to the water, which will at least have the effect of correcting the peculiar acrid, musty odour generally noticeable in a room in which a case of measles is being nursed. The bronchopneumonia is undoubtedly communicable; and it is undesirable to nurse a child suffering from this complication in the same room with others, or to employ the same drinking utensils. The windows of the room should be shaded by day sufficiently to relieve the photophobia—too dark a room not only has a depressing effect upon the patient, but prevents accurate observation of his condition.

Since the microbes associated with bronchopneumonia are found to be present in the mouth in more than half the cases of measles, the use of antiseptic mouth-washes is indicated, and the practice appears to have been attended by good results. For this purpose a solution of boric acid (1 to 2 per cent) is suitable, and its use is not ungrateful to a patient old enough to employ it. In infants the solution must be used with a spray or syringe, and, in epidemics in which a special liability to ulcerative stomatitis or to diphtheria is noticed, the employment of antiseptic mouth-washes should be considered obligatory. Further, all precautions designed to prevent secondary infections of the respiratory system should be carried out with particular care in children who by reason of their tender age (six months to six years), or because they are the subjects of rickets or tuberculosis, are specially liable to respiratory complications of a severe type.

Mild cases of measles of the ordinary type do not call for any treatment beyond the observation of the above precautions. No drug is known to have any power in antagonising the specific process. The patient should be fed simply; and the greater the fever and the more severe the type of the disease, the more simple should be the diet. The liability to the occurrence of diarrhœa should be borne in mind, especially in epidemics in which this complication is frequent, or in hot weather, or in individuals disposed to intestinal catarrh. In a robust child a diet of milk and gruel is the best; but in weakly children it may be desirable from the first to give eggs, meat-juices, and perhaps small quantities of wine or brandy. The child suffers intensely from thirst, and it may be allowed to take freely of bland fluids, water flavoured with lemon juice or raspberry syrup, or a phosphoric acid drink containing 1 or 2 per cent of phosphoric acid and a little syrup.

Nervous symptoms, if accompanied by high fever, restlessness, and slight delirium, should be treated by keeping the patient lightly covered,

and by the application of cold compresses, an ice-bag to the head, or even cold affusion. Sleep may often be induced by applying a cool, moist compress to the trunk, or, in adults, by a pack to the limbs. Much relief is often afforded by rapid washing of the whole body with water or with water and vinegar. When the cerebral symptoms are more severe, especially when there is high delirium with rapid pulse and flushed face, the best treatment seems to be hydropathic, applied either by means of cold or cool packs, or by a short lukewarm bath (90° to 96° F.). A cold affusion to the head, during the bath or otherwise, will increase its calming effect. If necessary, such baths may be repeated several times a day, but the water should not as a rule be used below 82° F.: they will be found to exercise a considerable influence upon the temperature in children. Prostration need not be considered a contra-indication of hydropathic treatment, which on the whole is perhaps best applied by the use of packs, not necessarily of cold water. If the depressing effect of the packs is likely to be excessive, it may be diminished by adding brandy to the water in which the cloths are wrung. Every case must be treated upon its own merits; and it is prudent for the medical attendant himself to watch the effects of the hydropathic treatment, at any rate on the first few occasions of its application. In severe cases with continuous convulsions the action of the bath treatment or of the cold pack is uncertain: sometimes it appears to determine a fresh accession of convulsions; but, before abandoning it in serious cases, it is desirable to try the effect of cold affusions to the head. When there is great congestion of the face, pointing to general cerebral congestion, the application of leeches to the temples or mastoid process may give relief; but before applying them it would be well to try the effect of a cool affusion to the head, the trunk and limbs being wrapped up in a blanket. Severe headache may be relieved by the same mode of treatment, or, except in young children, by the application of a mustard poultice to the back of the neck. Constipation, which frequently attends the cerebral symptoms, should be treated by copious cool enemas, with or without the addition of castor oil. When relief has been obtained by hydropathic measures the packs or baths may be repeated at longer intervals, and their use may be associated with certain antipyretic drugs: of these the most valuable is quinine. The dose of the sulphate may be roughly estimated at about a grain three times a day for each year of the child's age, with a maximum for adults of twenty-five to thirty grains in the day. When diarrhœa is present Vierordt recommends tannate of quinine in doses about three times as great as those of the sulphate; it has the further advantage of being less bitter and more readily taken (in powder) by children. Bromide of potassium has been strongly recommended by Barthez and Sanné in high fever with marked congestion of the head or lungs, and in convulsions. Small doses of chloral may be of use when there is much excitement, irritability, and loss of sleep at the commencement of the disease; but if there be signs of weakness of the heart this drug should be used with care, or avoided

altogether; the same remark applies to antipyrin. The last-named drug, however, will sometimes give good results when the fever is high at the onset, with much excitement and sleeplessness: it may be given either in three doses during the day, or in one dose in the afternoon, when it will sometimes procure sleep. The maximum quantity which a child under twelve years of age should receive in a day ought not to exceed eight grains; and in all cases in which there are signs of cardiac weakness it is better to avoid internal antipyretic remedies altogether, or to give only quinine. In cases of the typhoid and asthenic form hydrotherapy is not contra-indicated, but should be used with discrimination. Henoch recommends hot baths or mustard baths, with simultaneous cold affusions to the head. Alcohol is a most useful drug to use in these cases in combination with the cold water treatment; it is a good plan to give a dose of good brandy or whisky a few minutes before a bath or the application of a fresh pack. Vierordt, who herein seems to reflect current German practice, strongly recommends in serious cases with marked heart-failure the subcutaneous injection, whenever the pulse fails, of a solution of camphor in oil (1 in 10; or for children under three years 1 in 20). From $\frac{1}{2}$ grain to $\frac{2}{3}$ or $\frac{3}{4}$ grain may be given in this way to a child of two to three years of age. The hypodermic injection of caffeine in similar circumstances may also give good results. The dose should be two to three grains dissolved with an equal quantity of benzoate of soda in sterilised water. In children about puberty, and in adults, strong coffee may be used instead of caffeine. Severe hæmorrhagic measles must be treated on the same principles as the typhoid form, but the results are exceedingly unsatisfactory.

Itching of the skin, which is sometimes very distressing, may be relieved by local rubbings with carbolic vaseline ointment; an ichthyol ointment (ʒi. to ʒiii.) is said not only to relieve irritation, but if applied early to abort the disease; I have, however, no experience of the treatment, which does not seem to have been generally adopted. During desquamation warm baths should be used, taking special precautions to avoid giving cold. One or two baths with soap and water should be given at the end of convalescence, before the patient returns to other children. *Epistaxis* does not call for special treatment except when very copious or continued. When not severe it will generally be readily stopped by the injection of hot water. If inspection shew that the bleeding comes from the front of the nose, the anterior part of the nose may be plugged with antiseptic wool smeared with some antiseptic ointment. The posterior nares ought only to be plugged as a last resource, as the plug quickly becomes extremely foul, and may determine severe pharyngitis or set up acute otitis media. *Laryngitis*, if severe, may be treated by frequent short inhalations of steam, or by the pulverisation of a one per cent solution of boric acid or common salt, and by the application of an ice-bag to the front of the neck. The patient should be encouraged to check the cough, and will be assisted by the use of a linctus containing a small quantity of morphine or codeine. Attacks of *paroxysmal cough*, or

laryngismus stridulus, will be relieved by very hot compresses, applied every ten or fifteen minutes until the skin is very red. Sometimes in young children much relief is obtained by the application of one or two leeches above the manubrium sterni. *Bronchitis* or *bronchopneumonia* must be treated upon the general principles which guide the management of these disorders when they occur independently of measles (*vide* vol. v. p. 36). The same remark applies to *diarrhœa*, which is sometimes extremely troublesome.

Much may be done to prevent the occurrence of *otitis*. In addition to the use of the antiseptic mouth-washes and gargles already mentioned, the nose and naso-pharynx should be cleansed with a warm solution of boric acid and borax, introduced into the nose by means of a coarse spray or by the gentle use of a syringe. This should be followed by the application of an antiseptic ointment with a camel's hair pencil. The child, if old enough, should be encouraged to blow its nose. In younger children, and in all cases in which deafness, or tinnitus, is present, the use of Politzer's bag, which clears the nose and naso-pharynx and the orifice of the Eustachian tube, has been recommended; but it seems to be open to the objection that infective material may thus be forced into the middle ear. Politzer, indeed, maintains that there is merely a condensation of air in the tube and tympanum, not a transference from the naso-pharynx to the drum-cavity: however this may be, I am indebted to Dr. Dundas Grant for the observation that the risk is abolished or greatly diminished if the naso-pharynx have been previously cleansed, in the manner described above. In his opinion the occurrence of pain in the ear is an indication that only the very gentlest inflation should be used. In such cases relief may be obtained by the instillation of a few drops of a warm watery solution of cocaine and atropine (2 to 3 per cent). If pain or deafness persist, or if inspection of the tympanic membrane shew marked congestion, puncture may give relief; and this operation ought certainly not to be delayed if pus be detected bulging the membrane forward. The wound made by the knife heals quickly. In some cases inflammation of the lymphatic glands below the ear may be associated with the ear disease; after the ear itself has been properly treated, belladonna fomentations over these enlarged glands will assist in preventing suppuration. After the subsidence of the acute inflammatory disturbance, politzerisation and attention to the naso-pharynx are called for if deafness persist. Otorrhœa is best treated by the insufflation of powdered boracic acid.

During convalescence the patient should be fed well, dressed warmly, and guarded from draughts when perspiring. It is not advisable as a routine measure to recommend change of air, especially in the winter, until three or four weeks at least after the disappearance of the rash.

Dawson Williams.

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D. W.

GERMAN MEASLES

By Dawson Williams, M.D., F.R.C.P.

Synonyms.—*Epidemic rose-rash*, *Rubella*, *Rubeola notha*; Ger. *Rötheln*; Fr. *Rubéole*.

German Measles, or Rubella, is a specific, infectious, eruptive fever characterised by a long period of incubation, slight prodroma, a rose-red papular rash of short duration, pharyngitis, and adenitis.

It is not possible to give an altogether satisfactory description of the epidemic disease to which the name German measles is commonly applied in this country. The existence of such a disease is denied by some authors (1), who would refer all the cases either to measles or to scarlet fever; while others believe that under this name are included two or more acute specific disorders, distinct from measles and scarlet fever and from each other. The opinion, at one time prevalent, that the disease is a hybrid of measles and scarlet fever appears now to be abandoned.

There seems, in fact, to be little reason to doubt that an acute specific disorder, usually presenting symptoms not unlike those of measles but sometimes more nearly resembling those of scarlet fever, does occur at irregular intervals in epidemics of limited extent; and that this epidemic disorder does not afford any protection against measles or scarlet fever.

Etiology.—The sufferers, as a rule, are children, mainly between the ages of five and fifteen years; and the sexes are equally liable. The disease has been chiefly observed in the northern temperate climates, especially

in Germany, Great Britain, and the Northern States of America. It appears to be rare in France and Italy. It has been said to be more common among the poorer classes, but this opinion is probably erroneous. Epidemics are not infrequent in public schools in this country. In England and Germany the disease is most prevalent in the spring and early summer; but in America, it is said, in winter and spring. The disease is commonly contracted by personal intercourse; there is indeed no clear evidence that the infection can be retained by fomites.

The incubation-period is not well determined. The interval between exposure to infection and the appearance of the rash is probably most often seventeen or eighteen days; but it may be two or three days more, or five, or even, perhaps, seven days less. A patient who has contracted the disease is capable of conveying the infection to others two or three days before the rash appears—that is to say, while he is himself quite free from any obvious symptoms of illness. The capability of infecting others remains during the presence of the rash, but declines rapidly, and in mild cases disappears in a week; though it may persist a little longer after more severe attacks, or, perhaps, when there is much desquamation.

Symptoms.—The prodromal symptoms are slight, and their duration is short, not more than twelve hours; or they may be absent altogether: on the other hand, in the more severe attacks the patient may for two or three days experience malaise, dulness, and headache, accompanied by some suffusion of the eyes, soreness of the throat, slight cough, pain in the back, and glandular enlargement.

Commonly the first symptom noticed is the appearance of a discrete, pink, papular rash behind the ears and about the orifices of the nose and mouth. Rarely in any case is the appearance of the rash delayed beyond the second day. In rare cases it appears first on the back or chest. It may extend very rapidly to the trunk and limbs, or more slowly—possibly even with distinct intervals, so that there are two or three crops; in either case it may have faded on the chest and face before invading the limbs. The character of the eruption may vary in different cases, and in the same case at different stages. At first it consists only of slightly raised papules, which disappear on pressure, and are of a bright rose-red colour. The spots are lighter in colour, have less defined edges, and are more widely scattered, at any rate at first, than in measles; and they are not arranged in a crescentic manner. The rash in any particular area may begin to fade in a few hours, and fading is seldom delayed beyond twelve hours; but before this occurs the eruption may undergo a marked change, owing to the spread of a bright red flush on the face and neck, while at the same time the limbs become covered by a fine punctate rash indistinguishable from that of scarlet fever. The rash is not accompanied by any itching. The temperature in mild cases rises to 100° or 101° F. when the rash appears, and it falls to the normal about the third day as the rash finally fades. In more severe cases, especially if the catarrhal symptoms of the prodromal stage be well marked, the temperature

rises to 100° or 102° F. before the rash appears; going up one or two degrees when the rash comes out. In the rare cases in which serious complications occur the temperature may be maintained at a high level until they subside. The amount of catarrh which accompanies or precedes the rash varies greatly. As a rule there is some sore throat, accompanied often by enlargement of the tonsils; and a general redness of the palate and pharynx has been spoken of as an enanthem: the pharyngeal catarrh is more diffuse, and perhaps, in relation to the temperature and the general condition of the patient, more severe than in measles. The eyes are suffused and water, but there is little or no photophobia. A dry cough may be a source of some discomfort, but is far from a constant symptom. The patient may present some signs of bronchitis, which rapidly pass away as the rash fades.

In the great majority of cases there is little or no depression or sense of discomfort, and the patient may assert that he is perfectly well but for the rash on his face and a certain amount of sore throat. Enlargement of the glands, especially the posterior cervical, those behind the angle of the jaw, and along the sterno-mastoids, is almost constant: and in some cases those in the axillæ and groins will also be found to be enlarged and tender; though, as a rule, the patient makes no complaint. This enlargement of the glands about the neck is always an early symptom, and may be detected as long as a week before the rash appears.

Convalescence commonly begins as the rash fades; the catarrhal symptoms subside rapidly, but the enlargement of the glands may persist for a week or ten days or a fortnight longer. Desquamation does not occur in all cases. According to Dr. Clement Dukes, when the rash is most markedly of the measles type it is commonly very slight and branny, or absent; more copious, but still branny or in small scales, when the rash more nearly resembles that of scarlet fever. A slight rash is commonly followed by slight desquamation; a severe rash may or may not be followed by copious desquamation. The rule is, on the whole, that a severe widespread rash is followed by extensive desquamation, involving even the hands and feet. In mild cases desquamation may be over within a week. In such cases it should be looked for in parts of the person least exposed to friction, especially below the clavicles.

Complications and Sequels.—As a rule German measles runs its course without complications; when they occur they are of the catarrhal type. The angina may be severe and accompanied by the formation of false membranes on the tonsils; swallowing is then painful, and the child's life may be put in danger by the depression and interference with nutrition due to this cause. The bronchitis which sometimes accompanies the rash may be severe and persist after the rash fades, or bronchopneumonia may appear; pleuro-pneumonia has also been observed as a complication. Slight albuminuria, with some generalised œdema first noticeable about the face, has been observed in a few cases. The pharyngitis has sometimes been accompanied by laryngitis, and by

evidences of implication of the middle ear. It would seem that serious complications occur only in cachectic children, or in those specially predisposed to bronchitis and bronchopneumonia; in them only do chronic coryza and chronic enlargements of the tonsils and glands persist as sequels.

In some epidemics a few cases of **relapse** have been recorded, the intervals varying from a few days to two weeks or even more.

The **prognosis**, so far as the disease itself goes, is always good, and recovery is usually complete in a fortnight; though, even in healthy children, some general deterioration in health may remain. The only reservation is that in cachectic children, or in those already suffering from some serious chronic disorder, such as tuberculosis, a fatal termination appears sometimes to be determined by an attack of German measles.

Aberrant Forms.—Among the cases commonly classed as German measles there are some, which occur generally in groups, characterised by the absence of prodromal symptoms, by the very mild type of the general symptoms (the temperature being little if at all raised), by the absence of sore throat, coryza, or catarrh, and of enlargement of the lymphatic glands. The Council of the Medical Officers of Schools Association, in a circular, suggests that these groups of cases are really examples of an exanthematous disease distinct from rübella. The name "**infectious roseola**" or "infectious rose rash" is proposed as the designation of this disorder. The cases are met with most often in summer, and their characters are thus described in the document:—"The rash appears suddenly, usually with but slight fever, on the neck, limbs, and trunk; its distribution is irregular, and the face frequently escapes altogether. The eruption consists of large rounded areas of bright red, closely-aggregated spots scarcely raised above the surface of the flushed skin. It begins to fade on the parts first attacked as it extends elsewhere, and usually disappears within thirty-six hours, the slight pyrexia subsiding with it. There is scarcely any interference with the general health; the fauces may be slightly reddened, but there is no appreciable sore throat, coryza, or catarrh, and no enlargement of the lymphatic glands."

Dr. Clement Dukes believes that suffusion of the conjunctiva—**pink-eye**—may be the only symptom of an attack of German measles; though the patient may communicate the fully developed disease to others. He believes also, and there seems to me great probability in the suggestion, that German measles may give evidence of its existence only by producing slight feverishness and some enlargement of the lymphatic glands throughout the body. The suggestion is the more worthy of note as in France, where German measles would appear to be very seldom observed, some writers have described a "glandular fever" in children which is apparently infectious, but is clearly not the disease described under this name at p. 591.

Treatment.—An ordinary case hardly calls for any treatment by

drugs. The patient should be kept in bed, much as he may object—and commonly he will object much—until the rash has completely disappeared. Catarrhal complications should be treated as the like symptoms in measles. The patient should be kept in bed for, say, five days; for three or four days more he should be kept indoors; then, while still isolated, he should have as much fresh outdoor air as is possible. Desquamation does not contra-indicate outdoor exercise.

Diagnosis.—In the accompanying table are classified the symptoms upon which reliance must chiefly be placed in making the diagnosis between German measles, measles, and scarlet fever (2).

[TABLE

	German Measles.	Measles.	Scarlet Fever.
INCUBATION PERIOD	9 to 21 days, usually 18.	5 to 14, usually 10 (14 to rash).	Usually about 2 days.
PRODROMAL SYMPTOMS	Short and slight.	3 to 4 days, generally marked.	Brief: a few hours; rarely 5 days. Very rarely 7 days. Vomiting frequent.
KOPLIK'S SPOTS	Absent.	Present.	Absent.
RASH	First or second day, commonly first symptom, rosy-red dots. First, or early, about mouth.	Fourth day. Papular brick-red, or darker and crescentic, appear about mouth or forehead.	Dusky red and often diffuse. Skin burning.
CATARRHAL SYMPTOMS	Redness of throat, diffuse. Conjunctivæ suffused; watering of eyes slight. Bronchitis slight; bronchopneumonia rare. Diarrhœa absent.	Redness of throat, patchy at first. Catarrhal conjunctivitis. Much lacrimation and photophobia. Bronchitis usually marked; bronchopneumonia common. Diarrhœa frequent.	Throat affection proportionate to skin eruption. Dusky red. White plugs in tonsillar crypts. Conjunctivæ unaffected. Lung complications uncommon. Diarrhœa absent.
LYMPHATIC GLANDS	Generally enlarged, tender, and hard, including posterior, cervical, axillary, and inguinal.	Enlargement not marked early. Generally limited to those about the angle of the jaws.	Enlargement of neck glands proportionate to faucial affection.
GENERAL SYMPTOMS	Little or no depression. Tongue clean or slight fur; appetite often retained. Temp. may be normal. Pulse little altered, or accelerated in proportion to fever.	Depression generally marked, often much prostration. Tongue furred; little or no appetite. Temp. usually 100° or more. Pulse generally accelerated in proportion to fever; often weak and dicrotic.	With much rash; much depression. Tongue coated; peeling on fourth day, leaving "strawberry" tongue. Temp. always raised, often 105° to 106°. Pulse always accelerated, commonly out of proportion to fever.
ALBUMINURIA	Rare and slight.	Very rare.	Very frequent.
CONVALESCENCE	Rapid.	Commonly more protracted.	Often prolonged owing to complications.
DESQUAMATION	May be copious; always fine.	Seldom copious; fine.	Generally copious; in shreds.

Prophylaxis.—As the disease is certainly infectious before the appearance of the rash, isolation, to be effective, must be enforced before the disease can be diagnosed with certainty. Practically the only safe course is to separate all susceptible persons, who have been exposed to infection, from others who have not been so exposed, until the end of the third week after the date of exposure; if at the end of that time they are free from elevation of temperature, from enlargement of the glands, and from sore throat, they may be assumed to have escaped the disease. If this rule be followed, mistakes will very seldom, if ever, be made. As adults—whether because most adults have already suffered from a forgotten attack of German measles, or because the adult age does confer immunity—are little liable to the disease, this quarantine may perhaps safely be relaxed in their case. A patient recovered from German measles should not be allowed to mix with other susceptible persons until three weeks have elapsed from the beginning of his illness, nor until after he has taken a series of general baths to which some disinfectant may be added, though few are superior to soap, especially soft soap. Although there is no positive evidence that infection can be conveyed by clothes, the disinfection of those belonging to the patient appears to be a reasonable precaution. In mild cases, especially in those of the measles type, the period of isolation after an attack, above recommended, may be diminished by a week. Dr. Clement Dukes' experience is that, if disinfection be practised, the persistence of desquamation after the third week need not be held to render further isolation necessary.

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D. W.

SCARLET FEVER

By F. FOORD CAIGER, M.D., F.R.C.P.

The sections on Bacteriology and Hæmatology by LEONARD S. DUDGEON, M.R.C.P.

SYNONYMS.—*Scarlatina, Febris rubra*; Ger. *Scharlach*; Fr. *Scarlatine, Fièvre rouge*; Ital. *Scarlattina, Febbre rossa.*

Historical Survey; Prevalence. — The original habitat of scarlet fever is a matter of uncertainty, although from the earliest records on which any reliance can be placed, and from subsequent data, we are justified in assuming that the disease, at any rate for the past few

centuries, has shewn a marked predilection for European soil. It is asserted by Collie that scarlet fever existed in the time of Hippocrates, and indeed it has been assumed that the Plague of Athens was a malignant form of the malady, but the interpretation of the cases quoted in support of these opinions may be fairly called in question. Hirsch believes that the earliest definite record of scarlet fever dates from 1543, and he refers to an epidemic at that date in Sicily; it is stated by Haeser that the disease was briefly alluded to in the writings of Ingrassia of Palermo in the year 1550.

In the following century, however, we get upon firmer ground, for clear indications of its prevalence in Prussia during the first half of the seventeenth century are to be found in the writings of Doring and Sennert, and of Winsler and Fehr—although great confusion at that time existed between scarlet fever, measles, erysipelas, and (in all probability) diphtheria. This confusion was recognised by Sydenham, who, it seems, was the first to christen the disease "scarlet fever." His careful description of the disorder, as it prevailed in London during the years 1661 to 1675, not only laid the foundation of an accurate knowledge of its special characters, but at the same time clearly differentiated scarlet fever from measles, with which it had been hitherto confounded. Morton, however, a contemporary of Sydenham, continued to speak of the disease as "Morbilli confluentes," being evidently unimpressed by the distinction. Sydenham undoubtedly underrated the importance of scarlet fever, and even went so far as to say that it hardly deserved the name of disease; he had evidently never seen it in a severe form, and he makes no allusion to sore throat as a symptom of the affection. This seems all the more extraordinary, when it is remembered that so much confusion has continually existed between the diagnosis of scarlet fever and diphtheria, and, as Hirsch suggestively points out, the confusion of scarlet fever with other forms of throat illness has increased in proportion as the differentiation from measles has been recognised.

Since the time of Sydenham outbreaks of scarlet fever of varying severity have been frequent in this country; and its constant presence, in a more or less sporadic form, in the large towns of Western Europe has not been without its influence on the death-rate.

The continents of Asia and Africa, except in isolated localities, have shewn but little tendency to provide a field for scarlet fever, but America has been by no means exempt. The disease seems not to have reached North America until the year 1735, when it first appeared in Massachusetts; from thence it spread over the whole of the New England States, reaching New York in the year 1746. During the latter half of the eighteenth century outbreaks of scarlet fever are reported at irregular intervals in the states lying along the eastern and south-eastern shores of North America. In the year 1791 it penetrated into the interior for the first time, reaching Canada and the Northern States during the early years of the nineteenth century.

It was apparently not until the year 1830 that the disease obtained

a foothold in South America, since which time it has become generally diffused over the continent, where it often appears in widespread epidemics, characterised at times by considerable malignancy.

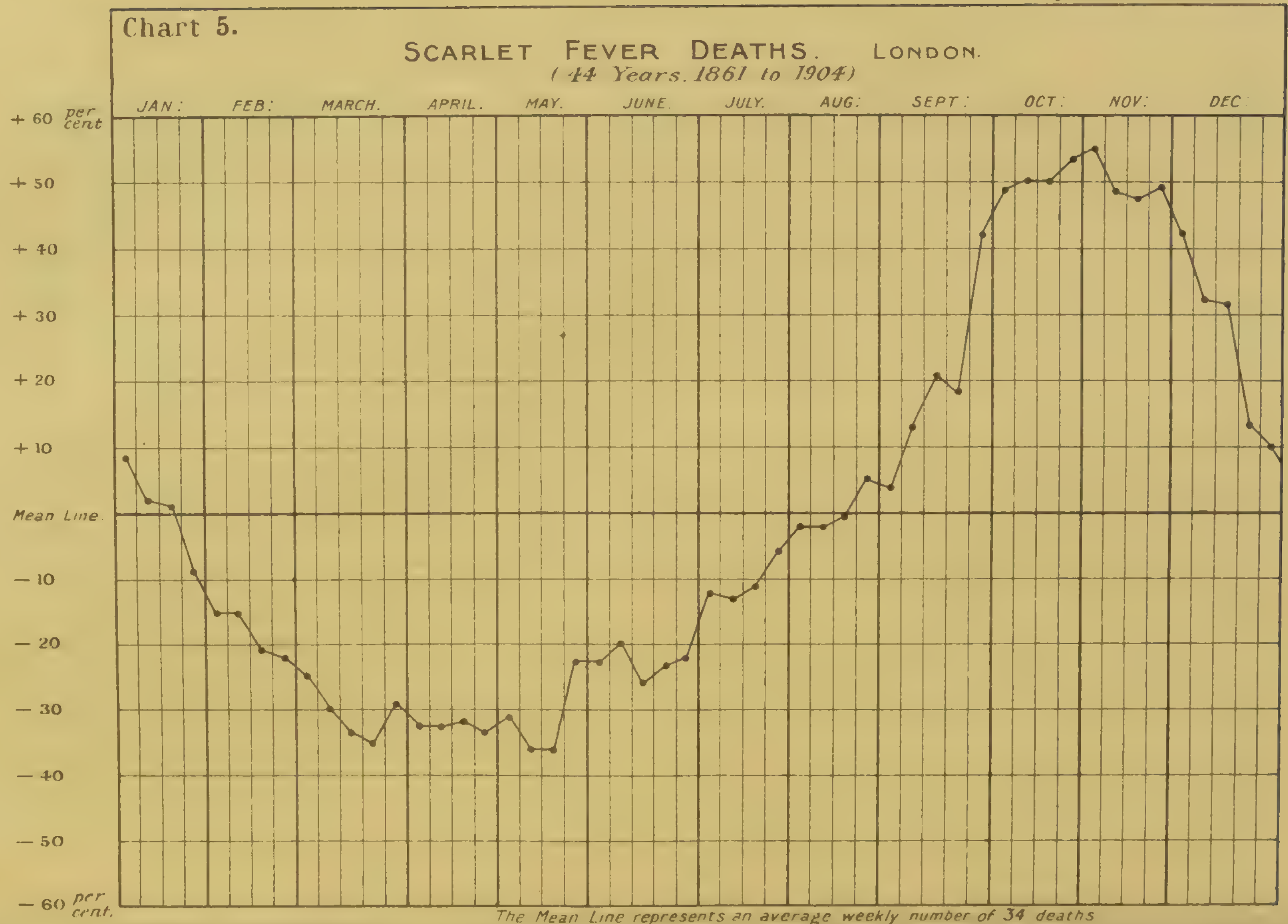
According to Hirsch, scarlet fever appeared in Polynesia for the first time in 1848; it arose simultaneously in New Zealand and Tasmania, whence it spread to the Australian continent a few years later.

On carefully surveying the records of scarlet fever epidemics in the past, it is manifest that nothing approaching periodicity has characterised its epidemic prevalence. Epidemics of the disease have occurred at irregular times, often separated by intervals of twenty years or more; but having once obtained a foothold, the period covered by the epidemic has usually extended over several years. Besides an absence of periodicity in the epidemic cycle of scarlet fever, it should also be noted that during the intervals there has not usually been the more or less complete disappearance of the disease, which we see in measles, small-pox, and typhus, but that there has been a tendency for scarlet fever to hang about the locality in a sporadic form, and occasionally, by the aggregation of cases, to constitute a minor epidemic.

The constant presence of scarlet fever in the north-western countries of Europe, and, with certain local exceptions, the equally constant immunity enjoyed by the tropical and subtropical regions of Asia and Africa, are as true of the present date as of old. That its comparative prevalence is in no way dependent upon the facilities of human intercourse is shewn by its complete absence in an epidemic form from certain countries which lie along the main routes of traffic throughout the world — such, for instance, as Egypt, India, Burmah, Ceylon, the Straits, China, and Japan, although its importation has been and is a matter of frequent occurrence. The prevalence of scarlet fever in an epidemic form on the continent of Australia is not common, whereas from the populous districts of North America it is practically never absent.

Although the epidemic prevalence of scarlet fever in the United Kingdom, as a whole, or even in any considerable district of it, is characterised by a marked absence of periodicity, yet in many large manufacturing towns, in which the disease is now practically endemic, a tendency has been apparent of late to the recurrence of a regular epidemic extension every few years. This may fairly be regarded in the light of a definite local cycle.

It is possible that during the last thirty years the prevalence of scarlet fever in this country has undergone some diminution, but trustworthy evidence on this point is difficult to obtain. The mortality returns, it is true, shew a progressive fall in the number of deaths, but as the type of disease, as shewn by the hospital fatality, has undergone a coincident improvement, no inference of any value can be deduced from them. The notification returns, which yield the only reliable information, shew that since the year 1890, when the Act first came into operation, as regards London, at any rate, there has been but little, if any, sign of abatement.



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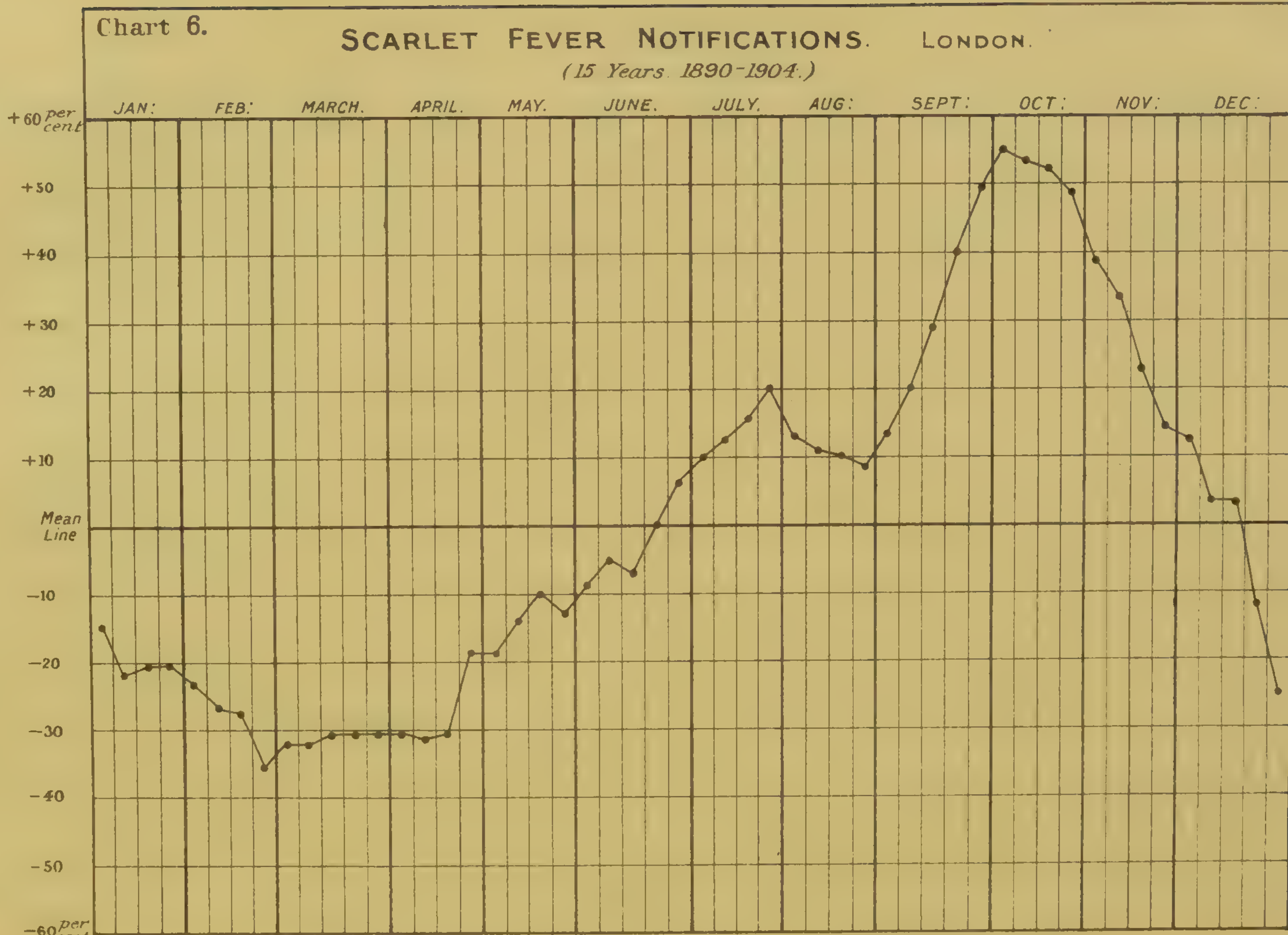

The Mean Line represents an average weekly number of 368·7 Notifications.

Dr Caiger – Scarlet Fever.

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TABLE I.—Average annual number of Deaths from Scarlet Fever per million living in successive quinquennia since the separate tabulation of Scarlet Fever.

Date.	England and Wales.	London.
1861–1865	982	1119
1866–1870	960	1147
1871–1875	759	575
1876–1880	680	624
1881–1885	436	426
1886–1890	241	244
1891–1895	182	239
1896–1900	135	737
1901	133	128
1902	148	121
1903	125	77

The comparatively greater diminution in the number of deaths in London than in the country at large since the year 1870 is in all probability due to the relatively large increase in hospital accommodation in the metropolis. The extension of the practice of isolation undoubtedly tends to lower the fatality of scarlet fever amongst the poorer classes, though its influence in checking the extension of the disease has been seriously questioned of late.

The dependence of scarlet fever prevalence upon season is more intimate, and the regularity of the association is most strikingly indicated, both by the records of large towns in which notification is in force, and by an examination of the Registrar-General's death-returns since the year 1860. In London valuable evidence of the seasonal prevalence of the disease is afforded by the monthly admissions into the hospitals of the Metropolitan Asylums Board, which now receive over 80 per cent of the scarlet fever cases notified in the town.

These records go to prove that in this country scarlet fever is least prevalent in the months of March and April; after which a steady rise takes place until the mean is passed at some time during the months of June, July, or August. A rapid extension of the disease occurs in September, reaching its climax usually during the month of October. From the beginning of November the curve shews a steady decline, dropping more rapidly during December until the mean is reached again, either towards the close of that month or during the first two weeks of January (see Charts 5 and 6).

The reason why the maximum occurs somewhat earlier in the year in Chart 6 than it does in Chart 5 is partly because the former signifies the

dates on which the cases were notified, not those on which the attacks proved fatal.

It will be seen that, roughly speaking, the prevalence of scarlet fever is above the mean during the last half of the year; and that it is below the mean during the first. Although this may be taken as characteristic of the behaviour of scarlatina in European countries, it by no means follows that the same holds good for all parts of the world. Indeed, Dr. Whitelegge states that in New York the seasonal curve of the disease is entirely reversed; and in Australia, a country in which scarlet fever is by no means widely prevalent, its diffusion is much more variable. The regular seasonal variation of scarlet fever is very suggestive of the operation of some climatic influence; yet it must be confessed that all attempts, and there have been many, to establish any definite association with either temperature, rainfall, or wind-direction have been signally unproductive up to the present.

Epidemic Type; Fatality.—All the records of scarlatinal epidemics in the past go to prove that the fatality of the disease in different outbreaks has been subject to enormous variation; and this opinion is confirmed, up to a certain point, by our own experience at the present day. This variation in fatality is marked, not only in epidemics widely separated both in time and locality, but also in outbreaks which have been simultaneously prevalent in contiguous localities. Moreover, it has been occasionally noticed that the type of attack has undergone a distinct change during the course of a particular epidemic, the usual tendency being for the attacks to become milder towards the close of the outbreak.

The type of the disease may, however, remain constant for many years in a particular locality; this is attested by the writings of Sydenham, who, as it would appear, had never met with a severe case in his own practice. Trousseau, too, reports that Bretonneau had never seen a death from scarlet fever in Tours from the year 1799 to 1822, but that in the year 1824 the disease prevailed in a most malignant form in the town and surrounding district. Graves, again, in describing the Dublin epidemic of 1802, states that the disease at that time prevailed in a very malignant form; but in the following year the type completely changed and a mild character was maintained through successive outbreaks for twenty-seven years, after which the disease resumed its former intensity. The same variation in severity has been found in the epidemics of scarlet fever on the continents of Europe and America; but in Australia it has been more uniformly mild. A notable exception, however, occurred in Melbourne in the year 1874, when the town was ravaged by an epidemic of great malignancy.

Many attempts have been made to trace a connexion between the influences of climate, season, soil, and locality and the type assumed by scarlatinal epidemics, but hitherto without success. Hirsch, however, while investigating the type of 265 epidemics in relation to season, found a slight preponderance of severity in the summer and winter months—a result by no means confirmed in this country.

The general mortality has varied, in different epidemics, from 2 or 3 to 30 per cent; and there seems little doubt that the severity of the disease in this country has been gradually diminishing during the last three decades.

As compulsory notification of scarlet fever has only been widely enforced since the year 1890, it is very difficult to obtain a long and continuous record of the case-mortality in any particular district. In London, however, the mortality of the cases admitted into the hospitals of the Metropolitan Asylums Board is of value in arriving at an estimate, as they now receive considerably more than four-fifths of the cases annually notified in the town. During the last thirty-four years 212,188 cases of scarlet fever have been treated with a combined mortality of 5·4 per cent; but since the year 1874 the annual percentage mortality has steadily fallen from 12·2 to 3·3. This reduction of mortality in recent years is no doubt partly due to an improvement in the average social status of the patients received. The latter figure, however, can hardly be taken as quite representative of the general scarlet fever mortality of London at the present day, as the cases sent into hospital still include the larger proportion of severe attacks.

A comparison of the number of deaths with the number of cases notified in the town, the only method for which complete accuracy can be claimed, shews that since 1890, when notification first came into force, the fatality of scarlet fever has gradually fallen to about a half.

TABLE II.—Shewing the Scarlet Fever Mortality in London calculated from Notifications and Deaths, and that in the Hospitals of the Metropolitan Asylums Board during the fifteen years, 1890-1904.

Year.	Notifications.	Deaths	General Mortality.	Hospital Mortality.
1890	15,330	876	5·71	7·86
1891	11,398	589	5·17	6·67
1892	27,095	1174	4·33	7·28
1893	36,901	1596	4·32	6·11
1894	18,440	962	5·21	5·92
1895	19,757	829	4·19	5·45
1896	25,647	916	3·57	4·29
1897	22,848	782	3·42	4·07
1898	16,894	582	3·44	4·12
1899	18,089	398	2·20	2·65
1900	13,800	365	2·64	2·97
1901	18,381	584	3·17	3·81
1902	18,252	556	3·04	3·45
1903	12,531	356	2·84	3·10
1904	13,439	36	2·71	3·37

The general case-mortality of scarlet fever in London at the present day would therefore appear to be about 3 per cent. Although the severity of scarlatinal epidemics in the past has by no means always

varied in direct relation with the social status or environment of its victims, it is nevertheless a matter of common observation that the disease affects with greater severity the inhabitants of those over-crowded districts of London in which poverty is rife and ill-nutrition common than it does the more affluent classes living in the comparative luxury of the west end and more open parts of the town. The aggregate type of attack in large towns is for this reason a very mixed one. Constancy of type is best seen in rural districts and amongst the inmates of large institutions. An epidemic of scarlet fever arising in a school or orphan asylum, or amongst the employés of a club or large business house, is usually extremely mild, either in virtue of a healthy régime or the favourable age of its victims. (For the personal factors influencing the case-mortality, see Prognosis.)

Spread and Infectivity.—The contagious element of scarlet fever is always derived from a previous case. In most instances it is taken by direct inhalation of the breath, or of air charged with minute droplets of mucus or saliva projected from the mouth or nose. In others, though probably more rarely, the disease is conveyed less directly by the desiccated discharges derived from the mouth, throat, nose, or middle ear. A rhinorrhœa or an otorrhœa occurring in connexion with scarlet fever is capable of retaining its infective properties for many weeks after the attack is passed, even though it may have been present before the disease was contracted. The infectivity of the minute particles of the cuticle shed during the earlier stage of desquamation can hardly be denied, though the part played by the skin in disseminating infection, at any rate during the later weeks of the peeling, is by no means as important as was formerly believed.

That scarlet fever is not spread to any distance by aerial convection is well shewn by the negative experience derived without exception from certain of the large fever hospitals which are closely surrounded by small tenements, for the most part crowded with young children.

It has been asserted that scarlet fever may possibly be transmitted by means of the urine in cases of chronic albuminuria, but its actual occurrence is certainly not supported by experience.

The virus may be conveyed by various articles which act as carriers, and the risk connected with cups, spoons, forks, tongue-depressors, and the nozzles of syringes which have been used for the patient must not be overlooked. Many instances have occurred in which the agency of books, clothes, linen, toys, furniture, bedding, parcels, and letters, as vehicles of contagion, has been clearly indicated. Such articles are capable of retaining the contagion in a potentially active form for long periods, certainly for several months, and possibly more, under such favouring conditions as aerial stagnation, moderate temperature, and the absence of daylight. When freely exposed to the destructive influence of light and air, however, they are speedily rendered harmless.

In certain rare instances it has been stated that infection may have been transmitted in a doubly indirect manner. A case in point is related

by Prof. Clifford Allbutt. A father, staying in the house of a friend, met, on the platform of a station thirty miles away, his son who came to this station from a school in which scarlet fever was then prevalent. The two spent an hour and a half together, and then returned to their respective quarters. Within the next four days the lady of the house to which the father returned fell ill and died of malignant scarlet fever. The father and the son remained well. Although the father made anxious efforts to find the cause elsewhere, no source of infection, other than that which suggested itself, could be discovered. Whether the infection here was actually transmitted in this way is certainly very doubtful, though, theoretically, the possibility must be admitted. The question at issue has a very direct bearing on the administration of a fever hospital. It has been suggested that the occasional occurrence of scarlet fever amongst the patients in a diphtheria ward is to be explained by the association of the nurses in the rooms which they share in common, for purposes of recreation and meals. The acceptance of this explanation would involve the assumption that the infection had been transmitted through two intermediaries, neither of whom suffered from the disease. The assumption appears to the writer extremely far-fetched ; the accidental admission into the diphtheria ward of an unrecognised case of scarlet fever, a contingency which is always liable to occur, affords a much more likely explanation. The possibility, however, that the disease may be transmitted through linen becoming infected in a laundry by contact with that of a person suffering from scarlet fever is a more practical one, and the risk through such contamination can hardly be ignored.

Scarlet fever is sometimes widely disseminated by means of an infected milk-supply, and instances of this mode of diffusion have been frequent of late years. Until the now historic outbreak in Marylebone, in the year 1885, it was universally believed that in these milk epidemics the milk was specifically contaminated from a human source—either directly from the hands of the milker, or from accidental exposure to the products of a case of scarlet fever at some point in its transit between the cow and the consumer. The careful investigations of Messrs. Power and Wynter Blyth, in the outbreak referred to, led them, however, to disregard the possibility of the milk having received its infective properties from any human source. The milk was known to have been supplied from a dairy-farm at Hendon, and, further, it was definitely proved to have been exclusively derived from certain cows which were suffering from a peculiar disorder. Dr. Klein, as a result of careful research, came to regard this disease in the Hendon cows as the key to the epidemic in Marylebone, and the evidence he adduces undoubtedly lends some confirmation to the belief that it was the analogue of human scarlatina. (See p. 421.)

If it be ultimately established that the lower animals are capable of developing the disease and transmitting it to mankind, it is evident that our views of the epidemic possibilities of scarlet fever must be correspondingly extended. Moreover, if Dr. Klein's teaching be confirmed, viz. that scarlet fever and the Hendon cow disease, though shewing considerable

variation in their clinical appearances, are due to the same micro-organism, it lends support to the statement of Thomas, that a disease corresponding to human scarlet fever has been met with in horses, dogs, cats, swine, and other domesticated animals. Without going so far as to deny the possible truth of this statement, I am convinced, by a somewhat extensive experience in this direction, that cats, at any rate, rarely, if ever, actively convey the infection of scarlet fever.

Scarlet fever has been successfully inoculated by several observers, notably by Stickler in America, who succeeded in setting up the disease in ten children by inoculating them with the pharyngeal mucus of a scarlatinal patient. Although the inoculability of scarlet fever has been demonstrated by these very questionable experiments, the method has no practical bearing on the spread of the disease.

The scarlatinal patient is capable of imparting infection from the very commencement of his illness, though apparently to a less extent than when the fever is fully developed, but the time at which his infectivity ceases is at present impossible to determine; and, moreover, it varies widely in different cases. It is a safe rule in practice to insist on six weeks from the appearance of the rash as the minimum period of isolation, after which the patient's release will depend upon the completion of peeling, a sound condition of the fauces and buccal mucous membrane, and the absence of discharge from the nose or ears, particularly if associated with any sore, redness, or excoriation of the nasal, oral, or buccal orifices. Of recent years the infectivity of the cuticle in the later stages of scarlatinal peeling has been seriously questioned; and it is now the common practice of many physicians, whose wide experience of the disease entitles them to be heard, practically to ignore the peeling in its later stages, and discharge their scarlet fever patients, when fit in other respects, quite irrespective of its progress. It is probable that for the majority of patients a six weeks' isolation is really unnecessary, and the period might be curtailed to the extent of one or even two weeks without any harm resulting. On the other hand, it is beyond dispute that in a limited number of persons the mucous membranes retain their infectivity for an unduly long period after scarlet fever, without there being any indications which might lead to its occurrence being suspected. It is well established, moreover, that as the result of catching an ordinary cold, the infective capacity of the naso-faucial tract may become reinforced to such an extent that a convalescent, in whom the signs we are accustomed to associate with infectiousness have long disappeared, may again become an active source of danger to the community. In view of this ever-present risk, and of our inability to detect such exceptional instances of protracted infection, it is wiser to err on the safe side, and insist on five, and in every case in which the patient is a young child, the full period of six weeks' isolation. Experience shews that in adults such undue persistence of infectivity occurs but rarely. The time-honoured notion that a scarlatinal patient should be regarded as infectious so long as any remnant of desquamation remains to be completed is gradually

dying out, though, like many another traditional belief, founded on a misconception and supported by a fictitious appeal to experience, it is extremely difficult to eradicate. It is true that in many instances an attack of scarlet fever has been rightly traced to contact with a person many weeks convalescent from the disease, and should that person have been found on examination to be desquamating, what more natural, in view of the widely accepted belief in the infectivity of late desquamation, than that the peeling should have been held responsible for the occurrence, rather than a discharge from the nose or ear, in amount perhaps so slight as to have escaped detection? The importance ascribed to the agency of the skin in disseminating infection has diminished in proportion as the infectivity of the discharges from the mouth, nose, and ear has become more clearly recognised. That the desquamating cuticle in the earlier stage of the disease may be concerned in spreading infection, there can be little doubt, but whether, apart from the comparative ease with which it may be conveyed in the air, the shed cuticle is more likely to do so than anything else which is constantly subject to contamination by the infective emanations from the patient's mouth and nose, is by no means equally certain.

As convalescence proceeds the risk of a patient's skin acting as a vehicle of contagion becomes progressively less, probably in association with the diminishing infective capacity of his naso-faucial mucous membranes. It is very doubtful whether the desquamating cuticle ever derives its infective properties directly through the skin. It is probable that the large epidermal flakes which finally separate from the hands and feet in the later stage of peeling are quite innocuous, despite the popular belief to the contrary. Still less reason is there to regard the second peeling which occurs in some cases as likely to be infectious, although there is good reason to regard that which follows the occurrence of a definite relapse of the disease as being no less a source of danger than the original peeling. Redesquamation is in most cases confined to the hands and feet.

"*Return Cases.*"—A certain number of scarlet fever patients, some 2 to 4 per cent, sent out from the fever hospitals seem to communicate the disease to other members of the household after their return home, in spite of the greatest care in coming to a decision as to their fitness for discharge, and in respect to their final disinfection. In about one-half of the cases the secondary attack occurs within the first week after the patient has returned, and in about three-fourths within the first fortnight. A right understanding of the conditions which govern the occurrence of these "return cases" is of the highest interest, and the subject has for some time past been engaging the serious attention of those responsible for the administration of our fever hospitals. Some noteworthy facts have been elicited as the result of careful investigations into the origin of "return cases." It has been ascertained that in a large proportion of such instances the primary infecting case was found to be suffering from a mucous discharge from the nasal passages, in some cases associated

with reddening or excoriation of the external nares, either immediately or within the first few days after the patient's return from the hospital. In a smaller proportion of cases either an otorrhœa, often intermittent in character, or some degree of faucial or glandular inflammation was present, and in the remainder, nothing abnormal could be detected. The frequent association of rhinitis with an infective capacity in the person affected with it is now well established, but the question as to how it is set up, and what relation it bears to the strictly scarlatinal factor in respect to infectivity is by no means conclusively settled. It is highly probable that even in the later stage of convalescence a latent infectivity of the naso-faucial passages is capable of being reawakened under the stimulus of a fresh inflammatory attack. In some cases, no doubt, this is brought about as the result of an ordinary cold caught at the time of discharge. Not infrequently, the inflammation so set up represents the recurrence of a complication which had been present at an earlier period of the illness.

The opinion is gradually gaining ground that some, at any rate, of these secondary inflammations of the nasal, faucial, or aural mucous membranes, which so frequently arise during the course of the scarlatinal attack, are due to a separate infection with micro-organisms derived either from a similar case, or from another patient suffering from a septic attack of the disease. If it be ultimately proved that such discharges are propagable in themselves, the necessity for rigid classification of scarlet fever patients during both the acute and convalescent stages of the illness will be apparent, if only with the object of protecting those in whom the infection has died out from the risk of again becoming a source of danger to the community.

Dr. A. Newsholme, who has devoted much attention to the subject, is inclined to disbelieve in the influence of "Hospitalism" altogether. He holds that the balance of evidence is in favour of the autochthonous origin of the infection which gives rise to these complications, and that their appearance, like the undue persistence of infectivity which characterises some attacks, is part of the inevitable natural history of certain types of cases. Dr. Newsholme argues that, having regard to the large number of cases which come into hospital with the complications already established, we are justified in ascribing a similar origin to these complications when they appear at a later stage of the illness.

It is only reasonable to assume that in most instances the organisms responsible for these complications are derived from the patient himself; but to contend that it is so in every instance, and *ipso facto* to deny the likelihood of their ever being contracted from an outside source, would be equally unreasonable. Having regard to the facility with which diphtheria, especially of the nasal variety, is known to spread amongst the convalescent children in a scarlet fever ward, it is fair to assume that in some instances, at any rate, the origin of these septic discharges is capable of a similar explanation. The contention that "return cases" are almost exclusively a hospital phenomenon, and that they are practi-

cally unknown in connexion with scarlet fever patients who are treated at home, is certainly unfounded. Unfortunately, reliable statistics as to the occurrence either of mucous discharges or of "return cases" in the latter group are not available. It is probable, however, that "return cases" do occur more frequently in connexion with hospital patients than in those who are treated at home, but there are good reasons why it should be so, apart from the question of segregation.

It is to be feared that "return cases" will occasionally arise in spite of the most scrupulous care, though it is probable that their number may be reduced by the adoption of measures which are calculated to maintain the mucous membranes of the scarlatinal convalescent in a healthy condition. That the peeling in its later stages is not responsible is fairly certain.

F. F. C.

Bacteriology.—Whether, by an exhaustive investigation on the bacteriology of scarlet fever, conducted on the improved lines of modern research, it will be possible to obtain any definite facts such as we possess in the case of enteric and certain other specific fevers, it is impossible to say, but there is no doubt that our knowledge of the bacteriology of this disease is very limited. As is well known, Dr. Klein (19) isolated from the tissues of patients suffering from scarlet fever a streptococcus which he called the *Streptococcus scarlatinæ*; and in 1885, while investigating an outbreak of fever among certain cows belonging to a farm at Hendon, he isolated, from the ulcerations of the teats and udders and from certain viscera, a streptococcus which he considered to be identical with the *Streptococcus scarlatinæ* (19). This observation was not only of great interest but also of very great importance, because the milk obtained from the affected cows was shewn to have been consumed by persons who subsequently developed scarlet fever. Dr. Mervyn Gordon (10) followed up these observations by a careful and most valuable research into the bacteriology of scarlet fever. Dr. Klein asserted that the most important cultural characteristics of his streptococcus were as follows:—(1) When grown in broth, the medium remains perfectly clear, but the organism forms either one or more coherent conglomerate masses at the bottom of the test-tube. On shaking the culture the growth is not dissociated, but rises in the fluid. (2) Litmus milk is acidified and clotted in a few days. (3) The tendency for a nodular growth to form on agar. (4) A low type of pathogenicity for mice and rabbits. Dr. Gordon noted that the conglomerate masses of the streptococcus growing in broth are so coherent that there may be great difficulty in making film preparations. The clotting of milk was also found to take place very rapidly, and the acidification to pass on to a stage of reduction.

Bacillary forms of this streptococcus appear to be especially well marked; in some instances the morphological characteristics were very similar to those of the bacillus of diphtheria. In agar condensation-fluid both the conglomerate masses and bacillary forms are well shewn, producing the so-called "lace-work pattern."

Dr. Gordon investigated ten cases of scarlet fever in the post-mortem room. Cultures were made from fifty-six sources. In forty-five instances a streptococcus was recovered, and on twenty-six occasions out of these forty-five, in pure culture. From four cases he obtained the *Streptococcus conglomeratus*. In the large majority of instances, therefore, a streptococcus other than that described by Dr. Klein was obtained. It appears probable that the *Streptococcus conglomeratus* isolated by Kurth from the scarlatinal cadaver is similar to the most common variety of "streptococcus" recovered by Dr. Gordon in the post-mortem room in his cases.

In twelve cases of ear-discharge associated with scarlet fever, streptococci were isolated from the discharge in six instances, but in no case was the *Streptococcus scarlatinæ* obtained. In two cases of rhinorrhœa also associated with scarlet fever, the *Streptococcus scarlatinæ* was obtained in two instances, in one case in pure culture, in the other, associated with the *Streptococcus medius*. In twenty-seven examinations of the throat also made by Dr. Gordon during all, but especially in the latter, stages of scarlet fever, the *Streptococcus scarlatinæ* was found on no less than twenty occasions. It would appear, therefore, that the scarlatinal throat is the chief habitat of this organism.

Dr. Gordon also made a careful investigation with definite dilutions of the tonsillar exudation in ten cases of scarlet fever, and obtained the *Streptococcus scarlatinæ* in every instance. In seven examples it was the only organism present, and the cultures were made from the diluted tonsillar exudation ($\frac{1}{50000}$-$\frac{1}{300000}$ c.c.). These are the main points in Dr. Gordon's valuable work, to which further reference will be made.

W. J. Class of Chicago, in 1889, described an organism which he considered to be the cause of scarlet fever. He found that the ideal medium for the cultivation of this organism was glycerin agar to which 5 per cent of garden earth had been added, the mixture being sterilised in the usual way. The organism he isolated is best described as a very large gonococcus. It was found to be Gram-negative and had a special tendency to become glutinous. He found it invariably in the throat secretion, blood, and scales of patients suffering from scarlet fever. It was extremely pathogenetic for mice, and produced a disease in pigs resembling scarlet fever. Class stated that the blood of a patient just recovering from scarlet fever inhibited the growth of this coccus, and considered that the specificity of this organism has been proved beyond reasonable doubt, and that the streptococcus has nothing whatever to do with the etiology of scarlet fever. Class's observations have been confirmed by others in America.

From this *résumé* it is obvious that the bacteriology of scarlet fever requires careful and extended investigation before anything further is written on the subject, and that the main question undoubtedly centres around the streptococci. At the present day further knowledge is more urgently needed about the streptococci than about any other organisms known to bacteriology.

The indiscriminate use of the word "streptococcus" is a matter for

serious regret, and it is to be hoped that in the future no organism will be labelled as the *Streptococcus pyogenes* until it has been subjected to a very careful study, and the same remark applies to every other type of streptococcus.

If "streptococci" are really the important agents in the bacteriology of scarlet fever, as some investigators consider, careful attention must be devoted to the investigation of simple and toxic cases of scarlet fever during life. It is probable that the septic cases really represent an infection with the class of "streptococci" which produce similar results in many other diseases—a view which is somewhat strengthened by post-mortem observations in fatal cases of this variety of attack. It is impossible, however, at the present time to accept the streptococcus described by Dr. Klein as the specific cause of scarlet fever, any more than we can accept the coccus of Class. The cultural characters of the *Streptococcus scarlatinæ* are not sufficiently distinct to warrant this organism being classed as a special streptococcus with specific functions. The most that can be said is that, with the improved cultural methods suggested by Dr. Mervyn Gordon, we may be enabled to decide whether previous observations on this subject are correct or not.

Dopter has found that the serum of patients suffering from scarlet fever may contain agglutinins for "streptococci" isolated from cases of erysipelas, septicæmia, and puerperal fever, as well as for the streptococci of scarlet fever, while the serum of patients suffering from erysipelas and many other infections may agglutinate the so-called *Streptococcus scarlatinæ.* On these grounds, this observer considers that we should reject the evidence so far collected in favour of a specific streptococcus for scarlet fever. It is doubtful, however, if these observations are of very much value, as the existence of specific agglutinins for the streptococci is at the present time very difficult either to prove or disprove.

Parasitology.—In January 1904, Mallory published his communication on "Protozoon-like bodies" found in four cases of scarlet fever. He observed these bodies in the protoplasm of the epithelial cells of the epidermis, between these cells, and free in the lymphatic vessels and spaces of the corium just beneath the epidermis. These bodies he classified under two divisions:—(1) Round or elongated and lobulated bodies which stained delicately but sharply with methylene blue. The "parasites" belonging to this class possessed a fine granular reticulum and usually a close meshwork. They were sometimes found to be vacuolated and were usually of small size (2-7μ). (2) The Radiate type. These were seen in the protoplasm of the epithelial cells of the epidermis, and also free in the lymph-spaces of the corium and in the vessels. In some instances these bodies formed small clumps. They varied in size from 4-6μ. The radiate bodies contained a central spherical body around which were grouped 10-18 segments, in some instances united, but in others sharply separated from each other at the sides. The autopsies of Mallory's cases were all made some time previous to his communication, namely, in 1897-98. Two of the four cases were of the severe toxic type,

while the other two were instances of septic scarlet fever complicated with diphtheria. In each instance the rash was present at the time of death. Mallory also examined six other cases fatal early in the disease, and many more which died during the stage of desquamation, but with a negative result. In four examples, pieces of skin were removed during life, but no bodies were seen. Blood-smears, the nasal and lacrimal discharges, and swab preparations from the back of the throat were all examined, but also with a negative result.

The technique recommended by Mallory is as follows:—(1) Fix small pieces of skin in Zenker's fluid. (2) Stain paraffin sections in a 5 per cent aq. sol. of eosin (yellowish, Grübler) for thirty minutes. (3) Wash in water. (4) Stain for twenty minutes in the following: methylene blue (Grübler), 1; pot. carb., 1; water, 100; take one part of this stain to four of water. (5) Wash in water. (6) Differentiate in 95 per cent alcohol until eosin colour returns in sections and nuclei are sharply defined. (7) Dehydrate, clear, and mount in the usual way.

Mallory summarises his communication as follows: "I wish to say that while I, personally, believe that these bodies are protozoa, and have an etiological relationship to scarlet fever, I am far from claiming that such a relation has been proved."

Pieces of skin from a fatal case of toxic scarlet fever in an adult male were sent to me by Dr. Caiger for examination. The rash was well developed at the time of death, which occurred on the fourth day of the disease. The skin was fixed in Zenker's fluid and in salt-formalin, and stained with the best of the parasitic stains, Leishman's.[1] I did not find any bodies such as Mallory has described, or in fact, anything abnormal which could be likened to such bodies. In skin from another fatal case sent to me by Dr. Caiger, I also failed to find any of Mallory's bodies. Field, however, found Mallory's parasites in five cases of scarlet fever which had died during the course of the disease, but failed to find them in the skin removed from four cases during life.

L. S. D.

Morbid Anatomy.[2]—The scarlatinal rash is characterised anatomically by an active hyperæmia of the cutis vera, attended with a certain degree of capillary stagnation and considerable inflammatory œdema. Transudation of leucocytes and of a variable amount of blood-pigment into the surrounding tissue next occurs, attended with a rapid proliferation of the cells of the Malpighian layer, which becomes considerably thickened in consequence. Sections of skin from a toxic case of scarlet fever in which death had occurred on the fourth day were cut and examined by Mr. Dudgeon, who reports as follows:—"These were stained by Leishman's

[1] I use a stronger solution of Leishman's powder in methyl alcohol than is recommended by Leishman—namely, one of 0·5 per cent; but, otherwise, my technique is according to his directions.

[2] I beg to acknowledge my indebtedness to Mr. Dudgeon for much assistance in the revision of this section.

method. I found large numbers of coarsely granular eosinophils in the epidermis, corium, and subcutaneous tissue, and also in the small capillaries. The varieties of eosinophils present were similar to those found by me in the thymus glands of children—*i.e.* (1) large eosinophils with dark, almost homogeneously stained nucleus; (2) similar cells with a pale, irregularly stained nucleus; (3) polynuclear cells. The last variety was seldom found, but the first and second varieties were present with equal constancy. Numbers of bacilli were seen lying in the epidermis and in the true skin. These organisms were large bacilli with rounded ends, and stained evenly throughout. I failed to find any evidence of capsule formation. The organism, of course, could not be identified."

Desquamation is brought about by the effusion of serum between the cells of the epidermal layer just superficial to the rete mucosum, in virtue of which their mutual cohesion is weakened, and actual separation occurs at the point of effusion. This is best marked in those papules which actually become vesicular. When the fluid contents have dried up, their delicate investments soon become ruptured in the centre, leaving a series of pinholes from which peeling extends centrifugally. The eruptive hyperæmia also induces a trophic change in the rete mucosum, which is characterised by excessive proliferation of its component cells. In this way the shed epithelium is rapidly renewed.

Although the hair-follicles are implicated to a considerable extent in the inflammatory process, it is a mistake to regard them as necessarily concerned in determining the minute papular elevations of the cutis which are so characteristic a feature of the eruption. Many of these unquestionably correspond in position with the inflamed follicles, but the greater number are quite independent of them. Moreover, the surfaces of extensive cicatrices which are entirely destitute of hair-follicles are occasionally observed to be more or less covered with puncta.

The faucial inflammation in simple cases is characterised by inflammatory hyperæmia of the mucous membrane, attended with an accumulation of leucocytes in its deeper parts. Proliferation and degenerative changes in the epithelial cells occur, and the exudation of fibrinous lymph. In more severe cases the superficial layers of the epithelium perish, and, by an extension of the process, more or less ulceration of the mucous membrane results.

The tonsils share in the inflammation to a variable extent; in some cases a slight degree of swelling, accompanied by adenoid proliferation and an increase of the follicular secretion, is all that occurs. In those of the septic type, on the other hand, extensive ulceration usually takes place, and small foci of suppuration may appear in the substance of the tonsil. The organs may slough *en masse*, and the necrosis by its extension result in widespread destruction of the pillars of the fauces, the velum palati, and the tissues comprising the upper part of the larynx. In such cases the ulcerated surface is found crowded with putrefactive organisms, which also invade the lymphatics leading down to the subjacent glands. These latter are infiltrated with inflammatory products,

and not infrequently suppuration occurs in their substance or in the surrounding cellular tissue. In addition to other micrococci concerned in purulent infection, the presence of streptococci can almost invariably be demonstrated in the lymphatics and neighbouring tissues.

It must be confessed that to the naked eye the post-mortem appearances in a fatal case of scarlet fever are neither striking nor constant. They necessarily vary with the type of attack, the stage at which death occurred, and the presence or absence of any definite complication.

Rigor mortis is usually well marked. In toxic attacks decomposition sets in early, and is remarkably rapid. In such cases cadaveric lividity usually appears before death. The blood is dark in colour, thin, and does not clot. The vessel-walls usually shew a considerable amount of staining, and minute subserous ecchymoses are not uncommon. Cover-glass preparations were made by Dr. Mervyn Gordon of the heart's blood in eight fatal cases of scarlet fever. In three instances no micro-organisms were seen, while in five "a streptococcus" was found. In two of the negative examples, however, "a streptococcus" was obtained from the heart's blood by cultural methods. In four of these cases bronchopneumonia was present at the autopsy, while in all but one instance there was evidence of one or more of the septic complications of scarlet fever.

The macroscopic appearances of the lungs, liver, spleen, and pancreas are indistinguishable from those seen in persons who have died from other forms of acute fever.

The appearance presented by the intestines in some cases of scarlet fever is negative, but in a considerable number an unusual amount of softening of the mucous membrane is present throughout the entire tract. Along with this is occasionally seen uniform swelling and softening of the lymphoid glands, which is usually better marked in the solitary glands than in the Peyer's patches ; but in some cases both are equally involved. In very rare instances this swelling of the glands proceeds to actual ulceration, giving rise to a distinct suggestion of enteric fever ; and, like enteric, the affection is commonly seen most distinctly in the lower part of the ileum.

The appearance presented by the kidneys shews considerable variation. In some, in which there has been no clinical evidence of nephritis, and even in a certain number in which the symptoms have been well marked, the kidney to the naked eye appears practically normal, with the exception of an undue amount of congestion throughout its substance,—an effect which may be observed in the kidneys of persons who have died from any form of acute fever. The capsule strips readily, leaving a raw-looking surface from which blood exudes freely. In the majority of cases of scarlet fever, however, in which death has occurred early in the disease, the kidney will present the following appearances : The organ is usually somewhat enlarged, sometimes considerably ; it is congested, especially in the zone corresponding with the bases of the pyramids, where, and also in the substance of the cortex, minute extravasations of blood are

often seen; the stellate veins on the surface are unduly turgid, and the capsule readily separates. The cortical substance on section, and also its denuded surface, is pale, opaque, and of a yellowish tint when washed. The Malpighian capsules are clearly defined on the surface of the organ, and, on section of the somewhat enlarged cortex, appear as minute reddish-brown specks: while the branches of the dilated interlobular arteries are seen as small oozing points dotted over the cut surface. If death occur at a somewhat later stage in a case which has been obviously complicated with nephritis, the kidney is usually somewhat increased in size, the swelling being mainly cortical. It is less congested, more opaque, and obviously fatty. The Malpighian tufts may still be defined, both on the denuded surface and on section; but they appear as yellowish dots, and blood can but rarely be seen to exude from them.

In kidney disease of considerable standing, say from six months to a year, the appearances presented by the organ are those of subacute interstitial nephritis. The kidney is smaller in size, the cortex usually being relatively diminished; the substance is firmer, and the capsule more adherent: no projection of the tufts can be observed on the free surface.

Microscopically, the characters of the scarlatinal kidney are those of a glomerular nephritis. The appearances are briefly as follows:—A vascular change occurs, comprising intense congestion of the Malpighian tufts and the smaller vessels of the cortex, attended with hyaline degeneration of their internal coat, and an increase of nuclei in the middle muscular layer. This leads to narrowing and obliteration of their channels in parts, and is especially noticeable at the junction of the afferent vessels with the Malpighian tufts, at which point thrombi are occasionally found. The cells of the supporting connective tissue, and those of the epithelial lining of the capsules, share in the proliferation, so that many of the capsules become so crowded with newly formed epithelium that their function becomes entirely arrested. Aggregation of round cells or leucocytes next occurs in the connective tissues surrounding the cortical vessels and Malpighian capsules, and to a less extent in the space intervening between the urinary tubules. This accumulation of leucocytes is most marked around the small afferent arterioles at a point immediately before they penetrate the Malpighian capsules. The circulation through the vessels is hindered by the compression to which they are thereby subjected, and the capsules themselves, being involved in the process, ultimately become greatly thickened, and some of them entirely destroyed. Cloudy swelling of the epithelium lining the convoluted tubes, the interior of the Malpighian capsules, and ultimately the straight tubes, sets in at an early date. The tubules eventually become more or less choked by the accumulation of cells shewing marked granular and fatty changes. Blood, too, is often effused into their lumen, and many of the tubes become filled with casts composed of either blood or epithelial cells in all stages of degeneration.

If death occur at a later stage in the disease the vascular changes will not be so obvious, but the most striking appearances will be found in the interstitial elements, combined with a variable amount of parenchymatous degeneration, proportionate to the intensity of the interstitial affection. The enlargement of the organ is dependent upon a great increase in the number of connective-tissue cells throughout the cortex, leading to considerable thickening of the Malpighian capsules, and more or less strangulation of their blood-supply; a certain number of them become obliterated. The ultimate state, if the integrity of the organ be not in part restored, is characteristic of interstitial nephritis: a greater or less degree of contraction takes place in the interstitial tissue, leading to cortical atrophy, and an abnormal adherence of the capsule. This change in the course of years may lead to a contracted granular kidney.

Considerable diversity of opinion exists as to whether the changes in the kidney above described are necessarily present in all cases of scarlet fever, even in slight degree. Dr. Klein (21) has described the presence of definite glomerular nephritis in twenty-three consecutive cases of scarlet fever, fatal at periods varying from two days to seven weeks; and in all of those in which the organs were examined, he found the renal changes to be associated with certain definite morbid appearances in the liver, spleen, and lymphatic glands. It does not necessarily follow, however, that the changes referred to are present in cases in which the attack is of a mild character. I am able to assert that in one case at least of early scarlet fever, in which death resulted from a cause unconnected with the disease, the kidneys on careful microscopical examination revealed no evidence whatever of glomerular or commencing interstitial nephritis. Excluding those cases in which the albumin is only present as a faint and transient trace, and those in which it would seem to be directly dependent upon the pyrexia, it is well to regard all instances of albuminuria arising during the course of an attack of scarlatina as due to glomerular nephritis of some degree, if only in view of the frequency of its observed occurrence.

Mr. Dudgeon recently submitted the kidneys from two cases of septic scarlet fever to careful microscopical examination. In each case he found very marked evidence of acute interstitial inflammation throughout the renal substance. The changes were indistinguishable from those which may be found in any septic condition, and certainly could not be regarded as dependent upon the specific action of the scarlet fever poison.

A granular change may be found in the heart-muscle in fatal cases of scarlet fever similar to that often met with during the course of any other acute specific fever or toxæmia, whether microbic in origin or otherwise. (Other manifestations of the scarlatinal poison are dealt with in the section devoted to complications, see p. 451.)

Predisposition, in respect to scarlet fever, will be found to vary with age, sex, state of health, idiosyncrasy, and previous attack. Of these strictly personal factors the first and last are undoubtedly the most important.

Age.—During the first year of life the liability to scarlet fever is not very great: but from the time of birth it shews a rapid increase until the maximum is reached during the fifth and sixth years. From this time onwards a progressive diminution of susceptibility sets in, which is continued throughout life. On reference to Table III., which deals with the age-incidence of 167,840 cases of scarlet fever treated in the Hospitals of the Metropolitan Asylums Board, it will be seen that considerably more than a third of the whole number fall within the second quinquennium of life, and nearly another third in the first; the remaining cases are distributed in the later quinquennia, of which the third claims considerably more than half. It will be evident, therefore, to what an extent early youth determines susceptibility to the disease.

TABLE III.—Shewing Incidence of Age, Sex, and Mortality of 167,840 cases of Scarlet Fever admitted into the Hospitals of the Metropolitan Asylums Board from 1892 to 1904 inclusive.

Ages.	Males.			Females.			Total.		
	Cases admitted.	Died.	Mortality per cent.	Cases admitted.	Died.	Mortality per cent.	Cases admitted.	Died.	Mortality per cent.
Under 1	891	197	20·2	745	157	21·0	1,636	354	21·6
1–2	3149	518	16·4	2909	468	16·0	6,058	986	16·2
2–3	5809	707	12·1	5431	640	11·7	11,240	1347	11·9
3–4	7802	683	8·7	7845	682	8·6	15,647	1365	8·7
4–5	8562	501	6·2	8894	464	5·2	17,456	965	5·5
Totals under 5 years	26,213	2606	9·9	25,824	2411	9·3	52,037	5017	9·6
5–10	31,829	822	2·5	35,480	847	2·3	67,309	1669	2·4
10–15	14,042	158	1·1	15,219	150	0·9	29,261	308	1·0
15–20	5,092	68	1·3	4,827	53	1·0	9,919	121	1·2
20–25	2,215	38	1·7	2,529	42	1·6	4,744	80	1·6
25–30	999	20	2·0	1,401	19	1·3	2,400	39	1·6
30–35	503	11	2·1	743	11	1·4	1,246	22	1·7
35–40	218	5	2·2	314	8	2·5	532	13	2·4
40–45	92	4	4·3	118	3	2·5	210	7	3·3
45–50	50	3	6·0	53	1	1·8	103	4	3·8
50–55	27	3	11·1	27	...	...	54	3	5·5
55–60	6	...	...	8	...	...	14	...	...
And upwards	5	...	...	6	...	...	11	...	...
Totals	81,291	3738	4·5	86,549	3545	4·0	167,840	7283	4·3

Sex.—The influence of sex is not very great. Females are attacked more frequently than males in the proportion of about seventeen to sixteen. This preponderance in respect to female attacks is seen in each quinquennium after the fourth.

State of Health.—The liability to scarlet fever is considerably increased by the presence or recent attack of any other acute disease; and to this rule the other members of the infectious group are certainly no exceptions

[see "Co-existence of Infectious Diseases"]. The liability is in all probability greatest in a person suffering from diphtheria. It is very doubtful whether a strumous, tuberculous, or other dyscrasia augments in any way the susceptibility to scarlet fever; although a predisposition is certainly engendered by the presence of any form of catarrh, especially if localised in the fauces. The proneness shewn by the inmates of a children's ward to take the infection of scarlet fever is a matter of common observation, and the almost uniform mildness of its manifestation has given a special significance to the term "Surgical Scarlet Fever." That a woman during her puerperium is thereby rendered more susceptible to the contagion of scarlet fever than she would have been if subject to any other lowering influence is at least doubtful. Although I am by no means convinced of the truth of the assumption, I would regard the occurrence of scarlet fever in a puerperal woman with the greatest anxiety. In most cases of puerperal scarlet fever the act of parturition is directly excited by the scarlatinal attack, and in view of the high fatality attendant on the condition every effort should be made to protect a woman from the risk of contracting scarlet fever during the later weeks of pregnancy, even though she may have previously suffered from the disease.

Idiosyncrasy.—The immunity enjoyed by some individuals who, though frequently exposed to its infection, have never at any time been attacked by the disease, is a curious fact. In some instances this immunity is shared by all the members of one family, and in certain cases would appear to be hereditary. Of the conditions regulating it, however, we have absolutely no knowledge. Experience shows that we are not justified in regarding such immunity as necessarily lifelong. Upon other families the disease seems to fall with peculiar severity.

Previous Attack.—The immunity conferred by one attack in most cases persists throughout life; but second attacks of scarlet fever, arising some years after a previous one, are not infrequent in persons in whom the genuineness of the primary attack was beyond dispute. (See p. 460.)

Incubation.—In the large proportion of cases in which it is possible to define the length of incubation with any degree of accuracy, the period between a single definite exposure and the first appearance of the febrile symptoms has been either two, three, or more rarely four days. In some well-authenticated instances the latent stage appears to have been less than forty-eight hours, but not much less. It is significant that in some of those cases for which an incubation-period of less than twenty-four hours has been claimed, the rash has not appeared until the third or fourth day of the recorded attack. The early sore throat from which the attack was dated may not have been a symptom of scarlet fever at all; a simple tonsillitis or faucial catarrh seems to render a person distinctly more susceptible to the action of the scarlatinal virus.

On the other hand, the period of incubation is sometimes as long as five days and, in rare instances, it is believed to have been six. It is sometimes loosely stated that the latent stage in scarlet fever may extend to the length of a fortnight, or even more, but such statements must be

received with caution. I have never met with an instance in which there was any valid reason to believe that the period had been longer than six complete days. The point is one of practical importance to parents, schoolmasters, and other persons concerned with the custody of children. To them it may be confidently stated that, if the first case be properly isolated and the necessary measures for disinfection scrupulously carried out, the safety of the other members is practically assured provided no second case arise before the end of a week.

Invasion.—The scarlatinal attack in most persons develops with considerable rapidity. In addition to the ordinary signs of the febrile state—such as chills, weariness, aching pains, coated tongue, loss of appetite, broken rest, etc.—there are three symptoms which, in the frequency of their observed association, are eminently suggestive of commencing scarlet fever. These are sore throat, headache, and vomiting; to which may be added, less decidedly, diarrhœa. Of these, sore throat accompanied by more or less submaxillary tenderness and a variable degree of painful deglutition, is probably the most constant: next to this, in adults, headache is the most frequent symptom. In young children vomiting is relatively more frequent than headache: diarrhœa, too, more commonly occurs in children, especially on the approach of a severe attack. An analysis of 1008 consecutive cases, in which the history of onset was inquired into, shewed that vomiting occurred in no less than 80 per cent. In this series more than 75 per cent of the patients were under ten years of age.

I have said that in a certain number of cases a sore throat may have preceded the other symptoms of invasion by several days, even a week. But in them a distinct aggravation of the throat symptoms is usually seen when the rise of temperature, vomiting, headache, and other signs of acute invasion supervene, and the early sore throat may very likely have been unconnected with scarlet fever, or but a disposing factor at best.

As a general rule severity of initial symptoms implies severity of attack, especially in respect to persistent vomiting, which is the rule in cases of the toxic variety. Some very mild cases exhibit a complete absence of prodroma; the rash may be the earliest and most prominent sign of illness.

Clinical Varieties.—Although no fast line can be drawn between one form of attack and another, yet for the purposes of clinical classification, and more important still, in reference to prognosis, cases of scarlet fever can generally be referred to one or the other of the three following classes—(1) Simple; (2) Septic; (3) Toxic. Of these the two latter are by far the most grave. It must be remembered, however, that individual cases vary much in the severity of their manifestations, and insensible gradations are seen on the confines of these classes.

1. *Simple Scarlet Fever.*—Otherwise known as Scarlatina Simplex or Scarlatina Benigna. A case of this, the most common variety, may be

expected to conform to the following brief description :—After the symptoms of invasion have persisted, usually with moderate severity, for about twenty-four hours, the characteristic scarlet eruption appears, being in most instances first seen on the neck and chest. In a considerably smaller number of cases the rash may be delayed even as long as thirty-six hours after definite invasion. It is attended with an aggravation of the throat symptoms, and the tongue becomes thickly coated. Faucial discomfort and more or less difficulty in swallowing are complained of, the attempt being attended in some cases with severe pain running up into one or both ears. Tenderness and a slight but palpable fulness of the submaxillary lymphatics are present in almost every instance. Along with the increase in faucial discomfort the rash continues to extend, the pulse to increase in frequency, and the temperature to rise, until a climax is reached on the third or fourth day of illness, by which time the tongue presents the characteristic strawberry appearance. Then, or a day later, defervescence sets in attended with a gradual improvement in all directions; the temperature and pulse steadily subside, the eruption fades, the throat symptoms abate, and convalescence is reached on the sixth, seventh, or eighth day unless interrupted by some complication. It may therefore be stated that the febrile stage in a well-developed attack of simple scarlet fever lasts about a week, and even before this time some peeling is usually to be found in certain situations.

2. *Septic Scarlet Fever.*—This form of attack, often designated Scarlatina Anginosa or Scarlatina Ulcerosa, most commonly affects young children. It is characterised by an ulceration, which, though invariably commencing in the tonsils, may by its extension lead to widespread destruction of the neighbouring parts. The process is attended with the gradual development of the symptoms of septicæmia. Briefly, the course of the attack is as follows :—After the signs of invasion (which are likely to be more pronounced than in the previous class of case) have persisted for some twenty-four hours more or less, the eruption appears. It is usually intense and somewhat dusky, often patchy in its distribution, and usually shews a tendency to staining, which may go on to the formation of definite petechiæ; with the development of the rash the temperature rises rapidly, and by the third or fourth day may reach 104° F. The tonsils are much swollen and the faucial mucous membrane acutely inflamed. The surface of the tonsils often presents necrotic patches of variable extent, or the tonsils may be covered with an exudation which is very likely to be mistaken for concurrent diphtheria (see p. 848). The tongue by this time will probably present the characteristic strawberry appearance. From this point the condition, instead of beginning to amend as in simple scarlet fever, continues with undiminished severity. The temperature remains high, and is of an irregular, remittent character. The exudation or superficial slough, if present on the tonsils, gives way to definite ulceration, attended with progressive infiltration of the subjacent lymphatic glands and surrounding cellular tissue. This brawny infiltration of the tissues of the neck is most distinctive of septic scarlet

fever, and if bilateral, may almost encircle the neck like a collar. A profuse muco-purulent discharge escapes from the nares, which become more or less blocked in consequence. In some of the more severe cases the discharge is thin and sanious, and by its irritant effect excoriates the skin surrounding the nostrils. By the end of the week the tongue again becomes coated and dry, the breath offensive, and diarrhœa often supervenes. During the course of the second week, unless improvement set in, the patient's state is usually aggravated by further changes. The temperature becomes of a more septic character, shewing diurnal variations of two or even three degrees; and the pulse more rapid and feeble, in young children being often over 160. Deglutition becomes more difficult, or, in consequence of progressive destruction of the parts, even impossible. Thus, food and offensive secretions may enter the larynx, and bronchitis or bronchopneumonia result. The condition of the patient at this juncture is deplorable in the extreme. Any attempt to swallow is attended with the passage of food into the nares. Sleep is impossible in consequence of the entrance of irritant secretions into the larynx. This may give rise to paroxysmal attacks of coughing, which are extremely painful by reason of the ulcerated condition of the structures forming the upper part of the laryngeal opening. In such cases no rest can be obtained, and the exhaustion and general prostration are extreme.

Towards the end of the second week a morbilliform eruption of septic origin may appear on the buttocks, cheeks, and extensor aspect of the larger joints; and the case may rapidly prove fatal. Death may not occur until the third or fourth week, in which case suppuration is very prone to arise in connexion with some of the lymphatic glands, or elsewhere. Further symptoms, which usually set in before death and afford evidence of the septicæmic nature of the case, are profuse diarrhœa, restlessness, delirium, sweating, pulmonary congestion, bronchopneumonia, wasting, and albuminuria. In cases which recover, the pyrexia and other symptoms usually shew a gradual abatement during the latter half of the second or third week; but even in these the duration of the acute illness is seldom less than a fortnight. Wasting is considerable, and convalescence, often interrupted by the advent of some well-recognised complication, is correspondingly protracted.

3. *Toxic Scarlet Fever.*—This form of attack includes those cases which are often described by the terms Scarlatina Maligna, Ataxic or Adynamic Scarlet Fever. The characteristic feature is that the gravity of the patient's condition is out of all proportion to the severity of the throat lesion. In the true malignant attack the patient is struck down by the intensity of the scarlatinal poison, and dies even before the typical symptoms of the disease have had sufficient time to shew themselves. The rash, if present at all, is patchy and ill-developed; there is but little affection of the fauces, the pulse is extremely rapid and feeble, and the patient, often conscious to the end, succumbs with the signs of profound nervous depression, and a temperature which, as in snake-bite, may have been subnormal throughout.

Such cases at the present day, in London at any rate, are extremely rare; whatever may have been the case in the past. Not infrequently, however, a type of attack is met with which by its toxic intensity is deserving of the name "Semi-malignant." It presents the following characters: the signs of invasion are unusually severe, especially the vomiting, which often persists throughout; the temperature soon rises to a great height, perhaps to 106° F., and is for the most part sustained, with but slight remission; the rash quickly appears, and becomes intensely vivid, with a tendency to cyanosis, best marked in the lips and extremities; petechiæ sometimes appear in the skin, which may become much discoloured in dependent parts; the fauces are vividly injected, and more or less œdematous, but there may be no ulceration whatever, nor any obvious infiltration of the subjacent lymphatics; the pulse is very frequent, often, in children, reaching 180 by the end of the second or third day. Vomiting, intense restlessness, muscular tremor, and mental confusion are usually present, the latter passing through the stage of delirium into final coma. Occasionally, however, especially in adults, the mind remains remarkably clear almost to the end. Death commonly takes place on the fifth or sixth day. Towards the end of these cases the temperature often shews a further elevation. It may register above 106° at the time of death. Cadaveric lividity always sets in rapidly, and signs of its approach are often noticeable before life is extinct. As in typhus fever, this condition simply represents the final development of a petechial eruption coupled during life with some degree of cyanosis, and may be regarded as an expression of the intense toxic hæmolysis.

It should be remarked that the term "malignant" is often loosely applied to that class of case which is here described under the name "septic." It is true that many of such cases, from one point of view, are malignant—indeed very malignant; but in them the dominant symptoms are dependent upon the relative severity of a local lesion which may be regarded as more or less contingent to scarlet fever. It seems to me more logical to restrict the term "malignant" to those cases which are malignant in virtue of the intense action of the essential scarlatinal poison.

Analysis of Symptoms.—*Aspect.*—The facial expression in scarlet fever, at any rate at an early stage of the attack, is usually intelligent. The eyes are bright and sparkling, and the conjunctivæ during the first two days are commonly somewhat injected, especially if the rash be well developed. The cheeks are from the first suffused with a vivid flush, which, on the second or third day of the eruption, becomes as it were dusted over with a fine white powder, giving rise to an appearance of powder and rouge which is very suggestive of the stage. This is in reality the earliest sign of peeling. In many cases the powdering is so fine that it might not inaptly be compared to the bloom on a ripe peach, and tends greatly to enhance the natural beauty of childhood. Its characters may be clearly defined by the aid of a magnifying lens. The forehead, too, is not infrequently flushed, but to a much less extent.

The region around the mouth is never invaded by a flush or rash of any description, but stands out pale and white in marked contrast to the vividly injected cheek. This circumoral pallor forms a well-defined circle or triangle, bounded laterally by the naso-labial folds, and below by the point of the chin. This, though by no means distinctive of scarlet fever, is of considerable diagnostic value as a point of differentiation from measles. After the fall of the temperature, and the decline of the rash, the complexion loses these characteristics, and the countenance generally becomes somewhat pallid. The pallor is partly the result of powdery desquamation, and is in some degree dependent upon a condition of post-scarlatinal anæmia. In very mild attacks, with slight eruption, these distinctions may not be apparent.

Eruption.—The scarlatinal rash is very characteristic, appearing usually within twenty-four hours after the symptoms of definite invasion; it is first seen on the chest, neck, and upper arms, from thence it spreads, in the course of a few hours, over the trunk, down the arms, and finally reaches the legs, extending from above downwards. In well-marked cases it usually reaches its height in three days, that is, on the fourth day of attack. Its full development on the lower part of the legs may be as much as twenty-four hours later than on the chest and neck. Its colour may be best described as a bright brick-red, varying in mild attacks towards pink, and shewing a tendency to the darker scarlet tints in toxic cases. Intensity and persistence usually go together, with a proportionate tendency to staining.

There are two elements in the developed scarlatinal eruption—a finely papular or so-called punctate element, which is usually the first to appear, and the last to go; and a superadded erythema, representing the confluent element. This is more transient, and usually disappears earlier than the fine papulation referred to. In many cases, however, the rash is of a mixed character from the outset. By careful attention to the relative development of the rash on different parts of the surface, it is usually possible to gauge with some degree of accuracy the stage at which the attack is presented. Confirmatory evidence of great value can also be deduced from the appearance of the tongue at the same stage. The rash when fully developed is attended with a considerable amount of inflammatory œdema, causing more or less difficulty in flexing the finger-joints.

The eruption fades in the order in which it appeared, going hand in hand with the rise and fall of the temperature. In well-developed cases the rash is gone by the end of the week, leaving behind a uniform greenish-yellow discoloration of the skin. This is best recognised by pressing with the finger on the surface of the abdomen, and then rapidly withdrawing it. In some instances distinct lines of hæmorrhage may be discerned for several days running transversely across the flexor surface of the elbows, wrists, and knees.

Certain local peculiarities of the eruption are deserving of notice. In the first place, it may be emphatically stated that a true scarlatinal

eruption is very rarely seen on the face; what is seen is, as has been stated, simply an erythematous flush, best marked on the cheeks, and often in less degree on the forehead. No punctation, still less papulation, is to be found in the vast majority of cases. The same distinction is true of the palms, and still more of the soles.

Although the distribution of the minute eruptive papules may be to some extent determined by the points of emergence of hairs, yet this is by no means necessarily so; for the majority of them do not correspond in locality with the hair-follicles, or, if so, only by accident. However, the local anatomical peculiarities of the skin are not altogether without effect on the development of the scarlatinal eruption. Where the skin surface is coarsely papular, as for instance on the outer surface of the upper arms and on the outside of the legs and thighs, it will be found that the rash is characterised by numerous coarse and indurated papules. These, however, may be normally present, in which case they are simply rendered more obvious by the hyperæmia which is an essential feature of the scarlatinal eruption. But although in their nature many of these papules may not be strictly scarlatinal, they nevertheless afford valuable indications of a recent eruption, as, by retaining their injection, they may remain unduly obvious for several days after the true rash has disappeared. The diagnostic value of this coarse papulation on the outer side of the legs and upper arms during the second week of scarlet fever can hardly be overestimated.

During the decline of the eruption the tension in the skin gradually relaxes as the œdema disappears, and a somewhat shrivelled, parchment-like appearance of the epidermis, especially on the hands and feet, affords a trustworthy indication of the peeling which is to follow.

In some cases, in consequence of the intensity of the rash, the minute papules which characterise the scarlatinal eruption actually proceed to vesiculation, and so give rise to localised crops of miliaria. They differ in their appearance from those seen in acute rheumatism in that each one is situated upon an obviously inflamed base. They most often occur upon the back of the hands, wrists, and forearms, more rarely on the neck, chest, and abdomen, and often give rise to considerable irritation.

Desquamation.—A certain amount of peeling of the cuticle will be found in all cases which have been attended with a distinct eruption. Whether peeling ever occurs in cases in which there has been absolutely no rash is, however, less certain. Its amount is usually proportionate to the intensity and persistence of the eruption. Desquamation bears the same relation to the antecedent eruption as peeling of the tongue does to the previous inflammatory injection of the mucous lining of the mouth and fauces. In infants, in whom the skin is soft and fatty, the subsequent peeling is usually but slight and transient, and, unless looked for with the greatest care, may escape observation altogether. It may be best observed by rubbing the skin with a towel after the child has been bathed, when delicate rolls of cuticle will generally be seen to come off

for several days after the rash has faded. Peeling, too, is often slight and ill-defined in adults who have passed through a mild attack. The only sign of its presence in persons in whom the skin is naturally greasy, as it often is in young adults who are the subjects of acne, may be a late separation in patches of the thick epidermis of the palms and soles.

The local peculiarities of the skin in different parts of the body exert a modifying effect upon the character of the desquamation. Thus, on the face and ears it usually takes the form of a fine powdering, and the same may be true of the groins, axillæ, and inner side of the upper arms. On the neck, trunk, forearms, and thighs the surface epidermis separates in the form of delicate scales or shreds of variable size, commonly preceded by a pin-hole or worm-eaten appearance of the cuticle which is very distinctive. From these numerous centres the peeling extends centrifugally, until, by fusion of their peripheries, any such arrangement is imperceptible. The skin covering the front of the knees usually desquamates in coarser scales and in less characteristic fashion. This is still better marked as regards the palms and the soles, from which the cuticle usually comes off in large thick flakes. In some instances these are so extensive as to resemble an incomplete glove or golosh; whereas in others, a dry and chalky appearance of the palms and soles is all that can be found to represent desquamation. It has been said that the nails are occasionally shed as a part of the general desquamative process, but I have never seen this occur.

The earliest sign of desquamation will be found on the face in the form of the fine powdering on the cheeks, which, if the subjacent flush be well marked, gives rise to the powder-and-rouge appearance before referred to. In many cases the powdering is of a coarser character, and may be earliest and best marked on the frontal eminences, the eyelids, the muco-cutaneous junction of the lips, the lobules of the ears, and at the margin of any scab or recent cicatrix wherever situated. In well-developed attacks the peeling may be visible on the face as early as the second day of the rash. It rapidly extends, and by the end of the week is well marked on the neck, chest, and inner surface of the arms. By the end of the second week peeling will have become more or less general. The face and neck by this time will usually have completed their peeling, and evidence of that which is to follow may either then, or a little later, be observed on the palms and soles, which feel dry and parchment-like, and present a somewhat wrinkled appearance. At the end of four weeks peeling in most cases will have been completed, with the exception of the palms and soles, which do not become clear as a rule until two or three weeks more have elapsed.

In some persons the period of desquamation extends to the length of three or even four months, but the majority will have finished their peeling in from six to eight weeks. Redesquamation not infrequently occurs, but is rarely more than partial.

A slight furrow running transversely across the nail often serves as an indication of a previous scarlatinal eruption. These depressed lines,

which not infrequently have a dotted appearance, may be seen above the bed of the nail during the course of the third week, and, rising as the nail grows, they usually reach the free border in four or five months. Though met with in other fevers, they but rarely reach the same degree as in many cases of scarlet fever.

Temperature.—Rising rapidly with the first symptoms of invasion, the temperature usually reaches its climax on the third or fourth evening of the disease, by which time the rash also will have attained its full development. After this the course of the temperature will vary with the type of attack. In simple scarlet fever it proceeds *pari passu* with the eruption, shewing a gradual decline until the normal is reached by about the end of the week, or, in very mild cases, a day or two sooner. During the first three or four days the diurnal variation is but slight, the evening temperature being usually a degree or two higher than the morning record. Throughout the lysis, which coincides with the latter half of the week, the daily excursion is commonly somewhat wider, shewing perhaps a difference of more than two degrees between the morning and evening records. In this form of attack the temperature but rarely reaches 105° F., even on the evening of the third or fourth day. It usually varies at this stage between 102° and 104°, and its subsequent decline is commonly more gradual than its previous ascent.

In the septic form of attack the temperature, instead of shewing a gradual fall to normal during the latter half of the first week, continues at about the same level; but the daily variations become wider as the septic features of the illness become more pronounced. Subsequently the course of the temperature will naturally depend upon the ultimate character of the attack. In favourable cases a gradual return to normal usually commences at some time during the course of the second week, and defervescence, even if uninterrupted by any definite complication, may take another week before it is complete. In the toxic variety the temperature is maintained at a higher level, and is less remittent. It usually averages about 104° F. Most of these cases, however, die without any abatement of pyrexia before the end of the first week. Indeed, the temperature may register 106° or more at the time of death.

It may be definitely stated that anything approaching a true temperature crisis in scarlet fever is an event of the greatest rarity.

Pulse and Respiration.—The only feature of the scarlatinal pulse which is deserving of mention is an undue rapidity, usually seen during the first twenty-four or thirty-six hours of the attack. This is best marked in those toxic cases which are attended with persistent vomiting and hyperpyrexia; but even in simple scarlet fever the pulse of a child of five years old may register nearly 160 per minute at the commencement, although the temperature may not be higher than 103° F. After the second day this character is usually lost. The arterial pressure is high, and the vessel more often feels small than the reverse. During convalescence an unusually slow pulse is occasionally observed in adults.

The frequency of the respiration seems to vary more with the height of the temperature than the rapidity of the pulse, and the expired air is highly charged with carbonic acid.

Fauces.—The typical scarlatinal throat is represented by a vivid red injection of the mucous membrane of the fauces, palate, and uvula, attended with some degree of inflammatory œdema, and more or less swelling of the tonsils. The degree to which the tonsillar swelling may attain is dependent upon the severity of a parenchymatous tonsillitis associated with the scarlatinal process; and its amount may be regarded, in a sense, as more or less of an accident. There is really nothing in its appearance to distinguish a scarlatinal throat, in mild cases, from a simple tonsillitis or faucial catarrh. The mucous membrane often presents an angry red appearance with a tendency to become dry and sticky.

In certain cases, especially those in which the inflammation is very acute, the surface of the tonsils may be coated with a pellicular formation, occurring either in patches or in a continuous layer. In rare instances the exudation may extend beyond the limits of the tonsils, and even encroach on the palate or side of the uvula. This must not be taken as evidence of co-existent diphtheria. In some cases it is obviously a thin exudation lying upon the surface of the tonsils; in which case it soon separates or becomes disintegrated, giving rise to a very superficial ulceration which rapidly heals. In others, instead of being raised above the surface, it is somewhat depressed, and represents a surface-necrosis of the tonsil, which separates later as a distinct slough.

In the septic form of attack the characteristic ulceration of the tonsils may originate in like manner; on the other hand, the process may begin as an ulcer, which, by its extension in all directions, leads to such widespread destruction of tissue that the mechanism of the parts is greatly interfered with. In exceptional cases a perforation of the palate occurs at a point just above the insertion of the anterior faucial pillar. The perforation is usually unilateral, but both sides may be affected. At a late stage of such an attack, any attempt to swallow results in regurgitation of fluid through the nostrils, and the entrance of food and offensive secretions into the laryngeal orifice. This not only leads to constant distress, but undoubtedly tends to rapid development of septic bronchitis and bronchopneumonia.

The offensive muco-purulent rhinorrhœa, so constantly present in septic attacks, is dependent upon ulceration affecting the naso-pharynx, whence, in consequence of the swollen condition of the tonsils, the discharge finds a more ready escape through the anterior nares. Should the naso-pharynx be the seat of adenoids, the ulceration is apt to be very intractable, and in perhaps the majority of cases in which a rhinorrhœa is unduly persistent, its continuance is dependent upon the presence of adenoids. These not infrequently slough.

Tongue.—Of all the symptoms in scarlet fever the tongue is perhaps the most characteristic. As in simple tonsillitis, the tongue rapidly

becomes coated with a thick, white creamy fur in consequence of an active proliferation of its normal epithelium. It then cleans with almost equal rapidity, and in well-developed attacks may become completely denuded of its epithelial covering by the end of the third day. Peeling of the tongue begins at the tip and edges, which, as early as twenty-four hours from the appearance of the eruption, may shew up red and raw-looking in marked contrast to the thickly-furred dorsum. Occasionally, even at this stage, the red tips of the fungiform papillæ may be observed peeping out through the fur which thickly covers the dorsum, and thus give rise to an appearance very similar to that of an unripe strawberry. Rapid separation of the epithelium then occurs, frequently in patches. The process of denudation, which commences at the tip and edges, extends centripetally; and by the third or fourth day the tongue is completely stripped of its epithelium, the region of the circumvallate papillæ being the last to clear. The tongue at this stage greatly resembles a ripe, red, and succulent strawberry. It may not inaptly be compared to the appearance of a piece of raw beef, especially if the surface become somewhat dry and glazed, which it frequently does when the patient has been asleep. Its strawberry-like appearance is greatly enhanced by the relative prominence of the fungiform papillæ. It must be remembered that the completeness with which the tongue peels is proportionate to the degree of inflammatory injection of the faucial and buccal mucous membrane. In cases which are characterised by very mild throat symptoms one does not expect to find so typical a development of the strawberry tongue. The value of the tongue as a diagnostic sign will be obvious when it is stated that no other form of sore throat whatever, but that due to scarlet fever, is attended with a clean, much less with a raw-looking tongue. Towards the end of the week the normal epithelial coat again begins to be restored, and, consequently, the tongue at this stage usually presents a somewhat silvery appearance.

In septic attacks the tongue during the second week again becomes coated, but not with the white, creamy fur so characteristic of the earlier stage. In severe attacks the organ not infrequently becomes affected with an aphthous-looking ulceration, which may also involve the gums and buccal surfaces of the cheeks and the lips; in this case it is not uncommon for the angles of the mouth to become sore and fissured.

In occasional instances the peeling of the tongue remains limited to the tip, the edges, and a longitudinal strip down the centre which often presents a somewhat ragged appearance. Gresswell, under the names "triareal" and "pentareal," has described certain peculiarities of the tongue which he met with in some cases. They are certainly exceptional, and, moreover, their relation with scarlet fever is at least doubtful.

Glands.—Some degree of enlargement of the glands lying beneath the ramus of the lower jaw probably occurs in all cases of scarlet fever which are attended with definite faucial inflammation. In most cases a

distinct fulness may be observed, accompanied by more or less tenderness on pressure. The pain experienced on swallowing is mainly dependent upon the pressure which is exerted upon these glands by the muscles during the act of deglutition.

In septic cases the glandular enlargement is considerable, and the tenderness may be acute. Suppuration, moreover, is not infrequent. In very severe cases the adenitis is often associated with a low form of periadenitis, and the infiltration of the cellular tissue may increase to such an extent that the neck becomes encircled by a collar of inflamed tissue, giving rise to the appearance known as "bull-neck." The swelling becomes red and brawny, and small foci of suppuration usually occur in its substance. If it be incised, the feeling to the knife is like that of cutting through hard bacon-rind; and a thin, blood-stained serum exudes which has strongly irritant properties. Occasionally portions of the skin break down, and sloughing of the subjacent cellular tissue may occur to such an extent that the deeper structures of the neck become exposed to view. Such patients usually die about the end of the second week, or a few days later; and I have more than once seen a fatal hæmorrhage occur in consequence of the wall of a vein becoming involved in the slough. Hæmorrhage from the perforation of an artery is excessively rare. An abscess not infrequently forms in one or more of the glands lying deep under the sterno-mastoid; in this case the suppuration is attended with considerable local swelling, and the constitutional symptoms are aggravated.

Nervous System.—In simple scarlet fever a variable amount of mental obscuration with a tendency to wander at night time is not uncommon. These signs are usually associated with a high temperature, and commonly appear on the third or fourth evening when the fever is at its height. It should be remarked, however, that the headache, pains, and vomiting which mark the early stage are also evidences of an affection of the nervous centres. In severe attacks the involvement of the nervous system is much more pronounced. In young children the attack may be ushered in with a convulsion; but though severe chills are sometimes complained of, a distinct rigor is decidedly rare. If the temperature be much elevated, delirium may appear as early as the second night of the attack, with a tendency to become continuous during the latter half of the week; in adults in these circumstances it may be of a violent character and necessitate some form of restraint.

During the course of the second week, as the strength fails, the delirium tends to become more of the muttering type. Muscular tremor, subsultus, and loss of control over the evacuations appear in bad cases. Towards the end the signs of cerebral exhaustion gradually merge into fatal coma, death being not infrequently attended or preceded by a rise of temperature which probably results from excessive disturbance of the heat centres. Delirium in young children is apt to be overlooked, as they are less accustomed to give expression to ideas. In them a blunted receptive faculty, coupled with restlessness and a

tendency to purposeless movements, may be the only signs of mental impairment.

In cases of the toxic variety the initial signs are usually very severe, and the vomiting may persist throughout. Muscular tremor is rarely absent, but in some cases a tendency to tonic spasm is indicated by some retraction of the head and the presence of more or less trismus. In others, an attack of general convulsions supervenes at a late stage, which usually terminates fatally. Though dull and confused in mind, if not actually delirious, the patient is apt to be intensely restless and to resent interference of any kind. The excreta are passed involuntarily, and the mental stupor soon passes into final coma. This form of attack, which in many points is very suggestive of typhus, is sometimes known by the name of "Ataxic scarlatina" in consequence of the profound affection of the nerve-centres. Temperatures of 112° F. and more have been recorded in exceptional instances; they are almost invariably fatal, and such a case is difficult to manage, as the patient resents both feeding and treatment.

The *urine* during the pyrexial stage presents the usual febrile characters. It is scanty, high-coloured, unduly acid, and contains, in proportion to its bulk, an excess of the normal solids. The chlorides, however, are diminished, if not entirely absent. During the first few days the amount of urea passed will be found to vary directly with the degree of pyrexia, a temperature of 103° F. being sometimes associated with the passage of urine containing as much as 4 per cent of urea. About the time, however, when the rash has reached its full development, usually the third or fourth day, this relation between the height of the temperature and the amount of urea commonly disappears. The urea then frequently shews a sudden drop to even less than 2 per cent, although the temperature may remain at the same height. In some cases, after the lapse of a few days, the amount of urea will again shew a temporary rise, although the temperature may have progressively decreased. During the height of the fever, the urine, as in other febrile disorders, not infrequently contains a trace of albumin, which quickly disappears as the temperature falls.

The sudden appearance of urine rendered smoky by the presence of blood is due to definite nephritis. Such, too, is the case if the urine be found to contain a progressively increasing quantity of albumin, even though unattended with hæmaturia. In these cases it is usually passed in somewhat diminished quantity at first, and contains a lessened amount of urea. At a later stage, however, more or less diuresis supervenes, and the daily loss of albumin is increased, although the total amount of urea excreted may still remain below the normal. The faint and transient clouds of albumin which frequently occur during the convalescent stage of scarlet fever have been the subject of considerable difference of opinion. These evanescent traces are certainly very common, occurring possibly in as many as 20 or 30 per cent of all cases. Whatever view may be taken of their pathology, they are apparently devoid of any prognostic significance.

With the onset of convalescence the urine gradually loses its febrile characters, and is excreted in greater quantity. It is pale and limpid when passed, but a nebulous deposit of mucus and phosphates usually forms at the bottom of the vessel on standing. The daily output of urea rapidly diminishes, attended with a corresponding fall in the specific gravity. The chlorides reappear at an early date, usually before the temperature has fallen to normal.

A slight degree of albumosuria is not very uncommon in scarlet fever, and should be remembered when testing for the presence of albumin.

A toxic body has been extracted from scarlatinal urine which, like that found in the urine of enteric fever, can only be regarded as a derivative.

The *bowels* are usually confined during the febrile stage, and may remain so as long as the patient is in bed; but diarrhœa is frequently an early symptom in sharp attacks. Diarrhœa, too, often appears towards the close of a septic case, and the stools then become exceeding offensive.

Skin.—In most cases which have been attended with a well-developed eruption the skin remains dry throughout, but in a certain proportion an imperfect diaphoresis occurs, leading to the formation of copious miliaria. Excessive perspiration often comes on after peeling is completed. It is best marked on the hands and feet, which frequently become bathed in sweat, both during sleep and under the stimulus of the slightest mental excitement. In adults this tendency may last for several weeks after desquamation is completed.

F. F. C.

Hæmatology.—*The Erythrocytes.*—From a systematic examination of the blood in scarlet fever patients Hayem, in 1884, found that after defervescence there was a decrease in the number of red cells by about 1,000,000 per c.mm. Kotschetkoff observed that a reduction of the red cells amounting to 2,000,000 per c.mm. or more occurred in nearly all cases. On the other hand, Zappert's observations did not shew such a definite oligocythæmia, for in only one of six cases was the count below 4,000,000 per c.mm.; other authors appear to have arrived at similar results.

The Leucocytes.—Kotschetkoff classified the leucocytosis of scarlet fever into three groups:—(*a*) Mild cases, 10-20,000 white cells per c.mm.; (*b*) Moderately severe cases, 20-30,000; (*c*) Very severe and usually fatal cases, 30-40,000. The leucocytosis is said to arise one to two days before the appearance of the rash, and to reach its height with the full development of the eruption. The polymorphonuclear neutrophils are also said to be increased both relatively and absolutely in all cases. Dr. Bowie, in 1902, published his observations on the blood in 167 cases of scarlet fever. He considers that the early eosinophilia which he has found might prove of value in the diagnosis of the disease from tonsillitis and septic conditions generally. He also states that if the number of

eosinophils be normal or subnormal after the first day or two of the disease, the case will in all probability be a severe one.

In conjunction with Dr. R. C. Jewesbury, I recently estimated the number of leucocytes per c.mm. of blood in 51 cases of scarlet fever. We also made a differential count of 500 white cells, and in each instance examined the blood for the glycogenic reaction. In one case we estimated the coagulation-time of the blood. The cases were all selected and classified from a clinical point of view by Dr. Caiger. Of these 51 cases, 44 were simple, 6 were septic, and 1 was toxic in character. Of the simple cases, 31 were mild, 5 were mild but also suffered from an inflammatory complication, 4 were fairly sharp, and 4 were somewhat severe.

One of the most striking features of the blood in scarlet fever is the appearance of the fresh blood. The appearance of a drop of blood at once indicates the nature of the attack. In the more severe, especially in the toxic and septic forms of the disease, the blood flows readily from the puncture, and appears to be more fluid than normal; it spreads on a cover-slip with extreme rapidity, and coagulates very slowly. The more severe the nature of the illness, the more marked are these phenomena likely to be. Similar results are obtained in ordinary severe inflammatory affections, but they are especially striking in scarlet fever.

Taking 6000 per c.mm. as the normal leucocyte count, a *leucocytosis* occurred in every instance but one. In eleven cases the total exceeded 20,000, so that a well-marked leucocytosis was found in just over one-fifth of the cases. In nine of these examples the illness was of the mild type. This agrees with the rule that the leucocyte count is no guide either as to the nature of the infection, or as to whether the lesion is inflammatory or suppurative. In only one of the cases with a count of over 20,000 was the attack septic.

The Polymorphonuclear Neutrophils.—Taking the normal relative number of these cells in human blood as 65 per cent, there was a relative excess in 42 cases, while an absolute increase was constant throughout our series. The greatest relative gain (over 80 per cent) occurred in thirteen instances. Of these no less than eight belonged to the mild variety of scarlet fever, and there was only one example of a septic case with a marked polymorphonuclear increase. Whether this was because the septic cases were treated with animal serums we are unable to state.

The Polymorphonuclear Eosinophils.—One of the most constant phenomena in suppurative and inflammatory infections is a relative diminution, and in some instances an absence, of this variety of leucocyte from the peripheral blood. In scarlet fever, however, the count of these cells is frequently considerably increased both relatively and absolutely. It is quite certain that we cannot obtain any absolutely reliable information as to the nature of the attack by determining the number of eosinophils in the peripheral blood. An absolute and relative (over 2 per cent) eosinophilia was found in the majority of the cases. In sixteen instances we obtained a

relative increase of over 4 per cent, and in two cases it amounted to over 10 per cent. In sixteen instances the relative number fell below 2 per cent, but in some of these examples there was an absolute excess. In the toxic case, in one severe case, and in one mild attack no eosinophils were found in the peripheral blood. In two of the septic cases, however, a marked increase, both relative and absolute, was present.

The Neutrophil Myelocytes.—In all specific fevers these cells may be found in the peripheral blood; in some instances in very large numbers. The variety of neutrophil myelocyte is practically always the cell named after Ehrlich. In seventeen of our cases a very small number of these cells was found to be present; the highest count only amounted to 2 per cent. The presence of the "myelocyte" was of no assistance in helping to form an opinion as to the severity of the illness.

Blood-Platelets.—An increase of the blood-platelets was seen in nearly every case, sometimes to an excessive degree.

Abnormal red cells, such as "ghosts," and nucleated red cells (normoblasts) were recorded in a few instances.

To summarise our results with the *glycogenic reaction* in 51 cases of scarlet fever, the best reaction usually occurs in the early cases, whether simple or otherwise; the septic cases may, or may not, shew a good reaction; some of the severe cases certainly do give an excellent reaction, but the reaction is not constant, and consequently this method does not afford reliable information as to the type of the attack. In clinical medicine it is of little value, but from a scientific aspect it is of undoubted interest. In scarlet fever, as in all other acute or chronic infections, the glycogenic reaction is valueless as a means of diagnosing suppuration.

In conclusion, an examination of the blood in scarlet fever is of little help in forming an opinion either as to the nature of the attack or of the ultimate fate of the case, with one possible exception, viz. the coagulation-time of the blood. Even this observation would be of little additional help to a physician with a wide clinical experience of scarlet fever.

L. S. D.

Aberrant Cases.—There is considerable difficulty in the diagnosis of many cases of scarlet fever by reason of an *unusual mildness* of the attack. The symptoms may be there, but yet are so ill-defined and transient as readily to escape observation. For their recognition an intimate acquaintance with the phenomena of the disease is essential, and also the opportunity of observing them at the right moment. Such attacks are most common in infants, and in adults who at some time previously have suffered from scarlet fever. Family idiosyncrasy, too, in respect to mildness of attack, is as well established as it is in the direction of severity. In some undoubted attacks the whole duration of the febrile stage may not last more than three days; occasionally it is even less. Though capable of imparting the contagion, the patient is

probably infectious to a much less extent than if the subject of a well-developed attack.

Excessive mildness is characteristic of those cases known as "Surgical Scarlet Fever," which so often arise in the wards of a hospital. That the type of attack should be so uniformly mild, is very possibly due to the fact that the patient, in virtue of a previous operation, wound, burn, or other breach of surface, or even that indefinite conjunction of ward influences known as "Hospitalism," is thereby rendered so susceptible that he reacts to a minimum dose of the contagion—a dose which, either by reason of its excessive smallness or its feeble virulence, might be quite inoperative in normal health. The term "Surgical Scarlet Fever" is somewhat misleading; the same mildness is frequently found to characterise the disease when it arises in the subjects of various medical ailments.

Again, certain cases of scarlet fever are aberrant by reason of the more or less complete *absence of one or other of the symptoms of the disease.* Thus the form of attack which sometimes affects nurses and others in frequent contact with the disease may be cited in point. Such attacks are known by the name of "Abortive Scarlet Fever," or "Scarlatina sine eruptione." As their name implies, they are marked by an absence of any eruption—sore throat, attended with fever of short duration and slight degree, being the only obvious symptoms. In other cases the eruption may be visible, but the faucial affection practically absent, and the tongue shew no sign of peeling whatever. This form of attack is most common in adults, in whom, too, the early rapidity of pulse is frequently wanting. In cases of the foregoing kind the later appearance of one of the recognised complications, especially mild articular rheumatism towards the end of the week (see p. 455), may assist in confirming a diagnosis otherwise doubtful.

An attack of scarlet fever may be aberrant by reason of its distinctive characters *being masked by the presence of another exanthem* (see p. 864). Thus, the eruption of scarlet fever may be blended with that of chicken-pox or measles, and in several instances I have seen the rashes of all three mingled in the same individual. Although the large majority of faucial exudations met with during the acute stage of scarlet fever are not diphtheritic, it is well to remember that the two diseases are occasionally co-existent; in such a case the special features of diphtheria are superadded to those of scarlet fever, and the combination is usually very dangerous.

When scarlet fever arises in a person who is at the time suffering from eczema or psoriasis, the appearance of the eruption may be very misleading. Irregular red patches of inflamed skin are presented on various parts of the body, which occasionally bear some resemblance to the rash of measles; but the raised patches are usually harsh and scaly, instead of yielding the soft velvety feel so characteristic of that disease. The subsequent peeling is excessive, and appears very early in the attack. Scarlet fever, arising in a strumous child who is suffering from con-

junctivitis, may, at an early stage, be very suggestive of the onset of measles, especially if the rash present the morbilliform conformation seen in certain cases which are characteristic in other respects.

Puerperal scarlet fever, that is scarlet fever arising immediately before or after confinement, is a conjunction which my experience leads me to view with the greatest anxiety, although I have noted with surprise that some physicians of experience regard it without much apprehension. It would seem that the danger to life enormously increases with the proximity to the time of delivery at which the symptoms of the disease appear. In my own experience of cases in which the rash appeared within four days of parturition the mortality has been over 70 per cent; and it should be remembered that the onset of labour may be one of the invasion-symptoms of the disease itself. This, however, but rarely occurs unless the woman has almost completed her full term. In puerperal scarlatina it is not that the strictly scarlatinal symptoms shew an undue severity, but during the few days following delivery, in spite of the most rigid antiseptic precautions, there is a great tendency to the gradual development of puerperal septicæmia. The rash in such cases is usually very intense, and the temperature remains persistently high. The sapræmic condition may lead to the development of coma, and the gradual failure of the heart's action without the intervention of peritonitis or other localised inflammation of a septic character. Such, at any rate, has been my experience in cases of undoubted scarlet fever occurring in conjunction with the early puerperal state.

Differential Diagnosis.—If attention be paid to the symptoms already described, a well-developed case of scarlet fever can hardly be mistaken for any other disease. In mild and ill-defined attacks, however, considerable difficulty may be presented by reason of their negative aspect. The diseases with which scarlet fever may most readily be confounded are tonsillitis, diphtheria, measles, German measles, and early smallpox; besides various other affections which may give rise to difficulty in exceptional instances. Influenza, simple febrile catarrh, erysipelas, the diffuse erythema which is apt to follow the injection of a curative serum or an enema of soap and water, especially if the erythema shew any trace of punctation, and even the rashes of belladonna and copaiba, have all of them been mistaken for scarlet fever.

From *tonsillitis* the diagnosis may be very difficult—in some instances quite impossible. It should be remembered that in tonsillitis there is usually an absence of vomiting, the skin appearance, if present, is represented by a simple erythema, limited usually to the chest and neck, and there is no papulation or even punctation. The swelling of the tonsils is often, for a time at least, more obvious on one side than the other; and, if other distinctive signs of scarlet fever be wanting, a high temperature may be taken as evidence in favour of simple tonsillitis. The tongue remains coated throughout, having a pasty appearance; and it shews no sign of peeling even at the tip and edges. The attack, moreover, is

rarely attended with rheumatism of the smaller joints, nor is it followed by desquamation.

Scarlet fever attended with faucial exudation may be mistaken for true *diphtheria*, especially as a redness of the skin is occasionally seen in the latter disease. Here, however, as in tonsillitis, it is simply a flush devoid of any punctation. It is usually limited to the chest, neck, and arms, and is very transient. (For other points of distinction, see p. 845.)

From *German measles* the diagnosis may be by no means easy. In this disease reliance should be placed upon the slightness of the pyrexia, and the absence of vomiting, headache, or any peeling of the tongue. The faucial affection is very slight, mild catarrh is frequently present, and also a tenderness, often complained of by the patient himself, of the posterior cervical glands, especially those lying over the mastoid and occipital bones. Some enlargement of these glands is common in scarlet fever, but usually to a less extent. In its early stage the rash of German measles usually conforms more to the measles type, though the spots are commonly smaller, more discrete, and pinker. In a few hours, however, it tends to become more diffuse, and may then entirely lose its morbilliform characters. The spots, moreover, are frequently seen upon the face and forehead, and even the circumoral region may be invaded. Slight desquamation of the trunk and limbs may follow, but the peeling never shews the pinhole conformation.

It has long been recognised by those who have devoted attention to the study of the exanthemata that many cases of what is generally regarded as German measles bear a close clinical resemblance to mild scarlet fever, so much so, that it is customary to recognise the existence of a "scarlatinal variety" of that disease. It is contended by Dr. Clement Dukes that the usually accepted opinion as to the nature of these attacks is erroneous, and that they are instances of a disease specifically and etiologically distinct both from German measles, with which it is not infrequently prevalent, and from scarlet fever, which it even more closely resembles. Dr. Dukes is of opinion that outbreaks of what he has provisionally termed "*the fourth disease*" are by no means uncommon, and that the reason why the affection is not more generally recognised is that it is usually mistaken for scarlet fever. He admits that it is frequently quite impracticable to identify the disease in isolated cases, but holds that in a series of attacks the diagnosis should be conclusive.

The chief clinical distinctions on which Dr. Dukes lays stress in the differentiation of "fourth disease" from scarlet fever would appear to be the following: The length of incubation, which has a probable range of from nine to twenty-one days. The relative, or even complete, absence of premonitory symptoms, the rash being often the first sign of illness. The slight degree of faucial inflammation and discomfort, inspection revealing little more than redness, with slight swelling, and a velvety appearance of the surface. The more rapid development of the rash, which, though closely simulating that of scarlet fever, is said to yield very much less sensation of heat to the touch. The amount of desquama-

tion, though liable to be as complete and copious as in any case of scarlet fever, bears no relation to the intensity of the rash, and the cuticle tends to separate in small scales, rather than in flakes or sheets. The tongue does not become coated with a thick white fur, and never assumes the typical strawberry character. There is not any special involvement of the lymphatic glands of the throat and neck as the result of faucial inflammation; the lymphatic glands universally are somewhat enlarged, hard, and tender, those in the posterior cervical, axillary, and inguinal regions being mainly affected. The pulse is not unduly accelerated in proportion to the degree of pyrexia, and the temperature tends to run at a lower level, and more speedily reach the normal. The sensation of illness, if apparent at all, is usually very slight; the symptoms, even in the more severe attacks, pass off in a few days, leaving comparatively little malaise behind. There is no liability to nephritis or other complication having a recognised association with scarlet fever. Further, it is stated by Dr. Dukes that, in the cases he describes as the "fourth disease," the patient ceases to be infectious at the end of fourteen to twenty-one days when disinfection has been carried out thoroughly, and that the attack confers no protection against scarlet fever.

Whether, on the evidence he has adduced, we are justified in accepting Dr. Dukes' contention that there exists a fourth disease, distinct alike from German measles and from scarlet fever, is, however, a question on which medical opinion is at present undecided.

At an early stage scarlet fever may be confounded with *measles*, especially if there be much conjunctival injection, and the rash be at all blotchy, or shew a tendency to aggregation of its papular constituents. In this case irregular tracts of raised and injected skin may be presented. In measles a definite history of two or three days' previous illness, with cough, sneezing, and lacrimation, can usually be obtained, but vomiting is usually absent. The course of the temperature varies in the two diseases; that of measles usually falls suddenly within forty-eight hours of the appearance of the eruption, instead of declining gradually with it. The catarrhal symptoms are a prominent feature throughout the attack of measles, whereas the throat affection is limited to an inflammatory redness of the faucial mucous membrane. A careful inspection of the buccal surface in a good light will usually reveal the presence of Koplik's spots, a sign which is of the greatest value in the early recognition of measles. Although the tongue often cleans rapidly, its peeling is rarely so complete as to give it a strawberry appearance; moreover, the rash usually affects the face, and has a marked tendency to invade the forehead and circumoral region; measles spots, too, are commonly seen at an early date behind the ears, and at the margin of the hairy scalp. During the course of the second week of a septic attack of scarlet fever an eruption of raised spots or somewhat larger blotches may appear, and give rise to the suspicion of an intercurrent attack of measles. They are often confined to the cheeks, buttocks, extensor surface of the larger joints, and parts which are subjected to pressure. The points which help to

distinguish a septic rash from that of measles are the following: The spots are commonly more raised; they are apt to be of a somewhat redder tint; and they are usually less persistent than is the rule in that disease. They frequently fade only to reappear in the course of a few hours, and can always be made to disappear on pressure.

The initial erythema seen in certain cases of *small-pox* is liable to be mistaken for scarlet fever, especially if generally diffused over the surface, as it often is in cases which subsequently become hæmorrhagic. In most instances, however, the efflorescence is confined to the lower part of the abdomen, groins, and axillæ. Vomiting is a common initial symptom in both diseases, but a definite rigor, though frequent in small-pox, is rarely seen in scarlet fever. Severe pain in the back, too, is very suggestive of the former disease, but the appearance of the true small-pox eruption on the third day, and the absence of peeling of the tongue, will settle any previous doubt.

The diagnosis of scarlet fever in the post-febrile stage will mainly depend upon the presence of characteristic desquamation, and the advent of some one or more of the recognised complications of the disease (see p. 451). It should be remembered that the tongue may retain more or less of the strawberry character for about a week after it has fully peeled; although it usually regains its normal appearance towards the end of this period. The coarse papulation on the outer side of the legs may remain visible for several days after all other signs of the eruption have disappeared, and slight staining may be observed on the trunk for a like period after a well-developed eruption has faded. A fulness or palpable enlargement of the glands beneath the jaw may remain for several days as evidence of a previous faucial inflammation. The diagnosis may be strengthened by ascertaining the mode of invasion, and whether the patient has or has not been recently exposed to the infection of scarlet fever. Inquiry also should be made as to the nature of any outbreak which may have been prevalent in the locality.

Prognosis.—In addition to any general consideration, such for instance as the epidemic type, or the slight possible influence which has rightly or wrongly been ascribed to season, the case-mortality is to a large extent dependent upon certain personal factors, of which the following are perhaps the most important:—

Age.—The fatality of scarlet fever is greatest in early childhood; it shows a progressive diminution from the first year of life until about the age of puberty. After this age the death-rate shews a slight and somewhat regular increase in relation to advancing years. By referring to Table III. (*vide* p. 429) it will be seen that the case-mortality during the first quinquennium is four times as high as in the second, and nearly ten times as high as in the third. The slight rise which marks the fatality of scarlet fever after the fifteenth year appears to be maintained through life, though the death-rate does not again approach the mean until about the fiftieth year.

Sex.—The influence of sex is not very great. The combined mortality

in males at all ages is greater than it is in females by ·5 per cent—the death-rate of the two sexes amongst the cases enumerated in Table III. being 4·5 and 4 respectively.

State of Health.—The unfavourable influence of the strumous or tuberculous diathesis is seen in the tendency which is often noticed in cases of pulmonary phthisis for a fatal issue to be hastened by an attack of scarlet fever, although the disease may have been previously latent, or at most have been pursuing a chronic course. So, too, a condition of bad nutrition, associated with poverty and a defective hygiene, undoubtedly disposes to a severe attack. This is shewn by the greater fatality which is found in scarlet fever amongst the inhabitants of the poorer districts of London, even though removed to hospital at an early date.

The tendency of puerperal women to fatal septicæmia as a direct consequence of the scarlatinal attack has been already referred to (see Aberrant Cases, p. 445). The subjects of previous renal disease are almost invariably affected with a recrudescence of inflammatory changes in the kidneys, which may lead to uræmia and a fatal termination.

Although the attack of so-called "Surgical Scarlet Fever" are usually characterised by excessive mildness, nevertheless it is not uncommon for those who are actually suffering at the time from some other infectious disorder to have the disease in a severe form. If the attack supervene during convalescence it is frequently of a benign character, and might deservedly be ranked amongst the so-called "surgical cases."

In addition to the increase of the gravity of a case of scarlet fever by the advent of any of the recognised complications, there are certain symptoms of the primary attack which are of unfavourable omen. Ulceration of the fauces, attended with glandular infiltration, rhinorrhœa, high temperature, and perhaps the appearance of a later septic eruption, are indications of the septic form which the disease is assuming. In the same way hyperpyrexia, extreme restlessness, and a vivid rash, accompanied by cardiac dilatation, a rapid, feeble pulse, early obscuration of mind, tremor, and persistent vomiting, are evidences of toxæmia, and of consequent danger to life. Delirium in scarlet fever always indicates a severe attack, especially when it occurs in adults, and is usually associated with a high degree of pyrexia. About 80 per cent of cases shewing a septic eruption are fatal, and a petechial eruption, with cold and cyanotic extremities, is an exceedingly unfavourable sign.

Complications.—Although most of the deaths attributable to scarlet fever are due rather to the severity of the attack in its acute stage than to any of its later developments, the complications of the disease are of considerable importance in view of the tendency of some of them to become chronic, and, if neglected, to lead to permanent impairment of health.

It is admittedly difficult when attempting to classify the various manifestations liable to arise in the course of a disease to draw any hard-and-fast line between complications and symptoms. Take, for instance, a common development such as *rhinorrhœa.* From one point of view it

is a complication, in that it complicates the normal course of scarlet fever, yet, on the other hand, it is one of the most constant and characteristic of the symptoms of a septic attack. If it be regarded as a complication, rhinorrhœa demands prominent notice, seeing that a discharge from the nose occurs more often than any other manifestation of which the occurrence is the exception rather than the rule in an ordinary attack. When the rhinorrhœa is of a purely mucous character, it is simply the expression of a catarrhal state of the nasal fossæ, a condition which is very liable to arise during convalescence, as the result, perhaps, of an ordinary cold. But when the discharge is muco-purulent, and, especially, if thin and straw-coloured, it is the outcome of a destructive ulceration of the posterior nasal mucous membrane. In the latter case the discharge is apt to be serous rather than mucous; it is of an intensely septic character, and, owing to its irritant properties, frequently gives rise to redness and excoriation of the external nares. The rhinorrhœa is apt to become chronic, and often proves refractory to ordinary medical treatment. In most of such cases the persistence of the discharge is due to adenoid growths in the nasopharynx. The important relation which has been shewn to exist between the presence of rhinorrhœa and protracted infectivity in the propagation of scarlatinal infection, has been already referred to. (See p. 419.)

Of the recognised complications the following table enumerates the most important. Those occurring in less than 1 per cent of cases are omitted from the table, but will be referred to later.

TABLE IV.—Shewing percentage incidence of Complications amongst 10,983 cases of Scarlet Fever treated at the South-Western Fever Hospital, Stockwell, during the years 1895 to 1904, inclusive.

Complications.	Number.	Percentage Incidence.	
Otitis	1650	15·0 per cent	
Adenitis	1253	11·4 ,,	
Rheumatism	743	6·7 ,,	
Albuminuria	878	7·9 ,,	11·9 per cent
Nephritis	441	4·0 ,,	
Tonsillitis (secondary)	342	3·1 ,,	
Ulcerative stomatitis	189	1·7 ,,	
Bronchopneumonia	114	1·0 ,,	
Relapse	128	1·1 ,,	

Otitis may arise at any stage of the scarlatinal attack after the first few days. Severe cases are much more liable to the complication than mild ones, and in such instances it usually appears earlier in the attack, namely, about the end of the first week of illness. It is an affection of early childhood, the liability decreasing with each year of life. After twelve to fifteen years of age it is very rare, but there is a tendency, even in adults, for old ear mischief to be lighted up by the scarlatinal

attack. Sex is without any influence here. This otitis may occur either in the form of a simple inflammation of the external auditory canal, with possibly more or less implication of the membrana tympani, in which case it is but a trivial affection of short duration; or, as is far more common, in the form of an otitis media, followed by a more or less profuse muco-purulent discharge. The collection of inflammatory products pent up in the tympanic cavity, if not let out by incision, will soon relieve itself by rupture of the membrane. That this affection is usually due to an extension of the naso-faucial inflammation along the Eustachian tube, with swelling of the mucous membrane and consequent narrowing of its calibre, would appear to be tolerably certain—at any rate when it arises early in the attack before the throat inflammation has subsided.

The distinctive signs of the affection are pain in the ear, tenderness over the cartilaginous portion of the canal, irritability of temper with more or less fever, followed usually after one to three days by rapid loss of the pain, tenderness, and fever on the appearance of the discharge. In a large proportion of cases, however, there is a remarkable absence of pain, the appearance of a discharge being the first indication. The glands immediately beneath the ear are usually somewhat enlarged and tender, and may remain so for several days. They occasionally suppurate. The discharge usually ceases after from two to four weeks' treatment, and the perforation rapidly heals; but in some instances cure may not be effected in less than three or four months. Should the otorrhœa unfortunately become chronic, the disease will in all probability be found to have involved the mastoid antrum, and unless an operation be undertaken for its cure the condition may ultimately result in serious intracranial mischief or pyæmia.

Occasionally, within a few weeks after the appearance of an otorrhœa an inflammatory swelling appears in the mastoid region, attended with a rise of temperature and acute tenderness over the apex of the bone. The swelling gives rise to more or less projection of the external ear. It is limited above by the temporal ridge, to which the fascia is bound down, and by its extension forwards leads to considerable œdema of the eyelids on the same side. The swelling is sometimes dependent upon suppuration of one of the posterior auricular glands, in which case the abscess is relatively superficial; or, more commonly, upon the formation of a subperiosteal abscess, which may be connected with carious bone and the presence of pus within the mastoid cells. In those cases of subperiosteal abscess, in which these parts are sound, it is possible that pus may have found its way from the middle ear by effecting a passage between the cartilage and the bony portion of the auditory canal. The firmness with which the thick fascia in the temporo-zygomatic region is bound down may effectually prevent the appearance of any œdema in this situation; and it is in some cases hard to realise that the source of what appears to be an independent œdema of the eyelids is really to be found, either in an inflammation of the middle ear, or of the mastoid bone on the same side. When suppuration has actually occurred in the swelling, a definite

ring of softening can be often detected over the subjacent bone at a point immediately behind the external ear. In the 1650 cases of otitis media in the foregoing table (*vide* p. 452) a mastoid abscess occurred in ·6 per cent.

In those somewhat exceptional instances of otitis media in which acute inflammation of the mastoid cells occurs during convalescence from an attack of scarlet fever, the symptoms are of considerable urgency if the tension be not relieved by the escape of inflammatory products into the middle ear or at the surface of the bone. Minute interstices in the osseous tissue of the mastoid, by means of which a communication between the interior and the subperiosteal surface is possible, exist in all subjects, but their patency and freedom of communication vary in different individuals, as does also the depth at which the antrum may lie from the surface.

The signs of *acute suppuration of the mastoid cells*—a condition which in young children is practically the same as empyema of the mastoid antrum—are briefly as follows:—Pain, and more or less tenderness, the latter occasionally intense, are complained of in the bone, together with local œdema and usually some redness of the skin. The discharge, though rarely completely arrested, is often diminished in quantity. The temperature, which may rise to 105° F. or more, shews wide fluctuations, and is often accompanied by an occasional rigor. The pulse is rapid and excitable, and in some cases markedly irregular. Great restlessness and irritability are present, and vomiting is common. The symptoms may rapidly abate and the discharge become freer, but they usually soon recur, often beginning with a rigor, and, unless relieved by operation, the case is likely to end fatally by meningitis, or by pyæmia after a more protracted and irregular course. I have seen one case in which the temperature reached 112° F. before death. The general symptoms of suppuration of the mastoid cells are not unlike those seen at an early stage in some cases of acute nephritis, occasionally there may be no local indications whatever pointing to affection of the mastoid.

It is well known that meningitis, intracranial abscess, both subdural and within the substance of the temporo-sphenoidal lobe or cerebellum, and general pyæmia, are all liable to supervene in cases of chronic middle ear disease. These conditions, like septic thrombosis of the lateral sinus, are events too remote to be considered here. The chance of their appearance in hospital-treated cases of scarlet fever should not be great; they are more prone to arise in patients who have passed through an attack of scarlet fever in their own homes, and in whom a septic condition of the middle ear has been allowed to establish itself.

Although I have only met with one case in which sinus thrombosis was definitely known to have supervened within a few months of the scarlatinal attack,[1] I have on several occasions found pus in the sigmoid

[1] Dr. A. K. Gordon of Manchester informs me that he has recently met with two instances in which this complication arose during the acute stage of a scarlatinal otorrhœa. Ligation of the internal jugular vein in the neck, together with the radical mastoid operation, in each case effected a cure.

groove between the sinus and its bony wall, the pus having worked its way backwards from the antrum which was full of it. That it is by no means infrequent to find true pus in the mastoid antrum after death, though its presence may have never been even suspected during life, would certainly suggest that its occurrence is much more frequent in cases of the septic type than is generally supposed.

Adenitis is a somewhat rapid swelling of one or more of the cervical glands, either behind the jaw or placed deeper under the sterno-mastoid, occurring during the stage of convalescence, the temperature having been normal perhaps for from one to three weeks. It is attended with a fresh rise of temperature, which lasts for a longer or shorter period, dependent on whether the gland suppurates, or, as more frequently occurs, resolves. In the latter case the temperature usually returns to normal within three days. Its fall, like its rise, is frequently somewhat sudden.

It is distinct from the glandular swelling occurring early in the scarlatinal attack, which is in some degree common to all cases with any throat affection worth speaking of, and may vary from a very slight glandular fulness up to the most severe glandular infiltration, attended with enormous swelling of neck and a profuse muco-purulent rhinorrhœa, all of which are directly dependent upon a septic ulceration of the fauces and tonsils. This condition is really one of septic adeno-cellulitis. It is not a complication, but part and parcel of a severe attack in its acute stage: moreover, it is due to an obvious primary cause, like the glandular swelling directly consequent upon pediculi or eczema capitis.

I refer rather to a primary pyrexial adenitis, occurring at a late stage of the disease, and unconnected, so far as can be seen, with any local exciting cause. In its pathology it would appear to be more directly related to those cases of sudden glandular swelling which arise as a result of what is called, for want of a better name, "taking a chill," whatever that really may be. These cases of adenitis are often seen to arise in groups about the same time in patients located in different parts of the hospital. They are met with in about equal frequency at all times of the year, and shew no clear connexion with either cold, damp, diet, or habits. Their occurrence in groups appears to suggest some widespread causative influence, such as some varying atmospheric or soil condition. Adenitis more often affects patients who are the subject of albuminuria, especially those with distinct nephritis. The complication is rarely met with after the fourth week of illness; it is more common in the second than the third, and in the third than the fourth. It is far more common before the age of puberty than afterwards, and is perhaps more frequent after severe than after mild attacks. It bears no relation to sex, and always terminates in recovery. About one-third of the cases suppurate; and it is always wise, in opening such a collection, to make use of a drainage-tube in view of the tendency to residual abscess.

Articular Rheumatism of sufficient intensity to give rise to elevation of temperature, pain, tenderness, and distinct effusion into the joints, is a

common complication. Its most frequent seat is the smaller rather than the larger joints: the arms suffer more frequently than the legs; the hands and wrists, than the elbows or shoulders; and the ankles, than the knees or hips. Most frequently of all it appears in the metacarpophalangeal joints, the fingers, and the wrists, but evinces a certain tendency to migrate. There are good reasons why it should be regarded as pathologically akin to ordinary acute rheumatism, though differing in certain respects. It is very prone to arise in persons who have been subject to attacks of acute rheumatism, although such subjects are in the minority. It shews, though in a less degree, the same tendency to move from joint to joint, and it is readily amenable in most instances to the action of salicin and the salicylates. On the other hand, it is less severe than ordinary acute rheumatism, its natural bent being more towards recovery; it is unattended with the acid perspirations and the creamy, furred tongue so characteristic of that condition; and it is less prone to affect the tissues of the heart or pericardium. Moreover, the joints are more prone to take on a suppurative action, leading to a condition of pyæmia, than in the ordinary rheumatic process.

Scarlatinal rheumatism is far more common in adults and in older children than in young ones, and affects females in a larger proportion than males. It arises independently of season or temperature, being as common in the summer and early autumn months as in the colder seasons. Its time of onset is remarkably constant, viz. the fifth, sixth, or seventh day of illness, at the time when the rash is just disappearing and the temperature falling to normal. It is more common in severe attacks than mild ones—in cases characterised by an intense rash and copious peeling—and it is in cases such as these, especially if of the septic type with ulcerated fauces, that the joint affection has a tendency to assume the suppurative form. The prognosis in ordinary cases is good. The cardiac structures are rarely involved at the time, probably in less than 3 per cent. Indeed, the occurrence of either endocarditis or pericarditis in the course of scarlet fever is very uncommon, though a soft systolic bruit may not infrequently be detected at the apex, even in mild attacks. These murmurs are very transient; they are apparently of hæmic origin, and are rarely indicative of valvular lesion. Definite pericarditis, however, is occasionally found to complicate a septic attack. In those exceptional instances in which the joints suppurate ["Scarlatinal Pyæmia"], the elbow, knee, and sterno-clavicular joints seem to be earliest and most frequently affected. Early evacuation of the joint, with antiseptic irrigation, is often followed by the best results.

Albuminuria.—Under this heading in the foregoing table (*vide* p. 452) cases of acute nephritis are not included, nor those in which but a faint and transient cloud of albumin was noted for less than three consecutive days. The urines during normal convalescence, unless any special indication existed, were for the most part tested three times a week; and in infants it was not always possible to examine the urine with regularity.

The incidence of scarlatinal albuminuria in patients treated in hospital

wards is not so great as is usually supposed. It must be remembered, however, that the inclusion of three or four beaten-up eggs in the diet of an adult will produce albuminuria by simple diffusion. In this series the amount of easily diffusible albumin given in the diet was not sufficient to yield signs of its presence in the urine, so that instances of albuminuria due to this cause were not to be expected. I believe that the albuminuria in which a faint cloud only could be obtained with picric acid for less than three consecutive days may be safely absolved from any prognostic significance: they do not shew any tendency to recurrence, nor does the urine on careful microscopical examination yield evidence of any renal product. But in albuminuria of greater degree, it is admittedly a difficult thing to draw a distinct line of demarcation between that which does and that which does not indicate acute nephritis, because cases of acute nephritis vary so widely in the severity and constancy of their symptoms. Nor must it be forgotten that certain very exceptional cases of nephritis are met with in which the urine, even on careful daily examination, has shewn no sign of albumin, though the clinical signs and post-mortem appearances are characteristic of the disease. Several such instances have occurred in my own experience. Pathologically, the difficulty of separating the two states is still greater, because the constancy with which kidney changes are present in cases of uncomplicated scarlet fever is a matter of dispute; and the opportunity of verifying the presence of substantive disease of the kidney in cases of simple albuminuria, so called, is of very rare occurrence.

I hold strongly to the belief that, although changes in the renal tissue are by no means necessarily present in an ordinary attack of scarlatina, yet simple albuminuria of any degree and acute nephritis, when they supervene, are due essentially to the same morbid process, varying only in intensity, or in the vulnerability of the kidney in the particular subject. The assumption that a simple albuminuria and a definite nephritis are both the expression of the same morbid action, varying mainly if not entirely in respect of degree, is supported by certain facts of their development. Their relative prevalence in a particular outbreak or in a particular ward is in agreement; they both tend to arise under the same conditions of environment: deficient ventilation, overcrowding of wards, especially with acute cases, climatic changes, chiefly in respect to atmospheric humidity, all have an apparent influence in determining the appearance of both. It may be noticed in passing that cold *per se* seems to be without influence; but cold in conjunction with damp is often followed by the appearance of fresh cases. They both shew a tendency to develop at the same stage of the illness, viz. during the latter part of the second, third, and fourth weeks (most frequently the sixteenth to the twenty-third day). The age liability also is in agreement, the susceptibility to both affections being fairly constant from the second year of life to the fifteenth, after which age cases of simple albuminuria are relatively more common than those of acute nephritis. That there is as great a tendency for cases of simple albuminuria to end in acute nephritis as

there is for cases of acute nephritis, if neglected, to relapse, is additional evidence in the same direction.

That kidney disturbance is less frequently met with in cases of scarlet fever treated in hospital than in those treated in their own homes, at any rate amongst the poorer classes, is very probable; and it is quite possible that this is in part because during their illness the patients are kept under more favourable atmospheric conditions: moreover, the action of the skin is encouraged by the employment of frequent and regular warm baths, begun directly the temperature has reached the normal, and continued during the stage at which the renal susceptibility is at its greatest.

Cases of "postural" or "cyclic" albuminuria are occasionally met with, and it is probable that their pathology is of a more complex nature. The large majority of patients who have been the subjects of simple albuminuria completely lose their albumin in a few weeks. I cannot call to mind an instance of a scarlatinal patient being discharged with albuminuria who had not previously had a definite attack of acute nephritis.

Acute Nephritis.—Although, as we have seen, it is not easy to draw a distinction between some mild cases of nephritis and those of simple albuminuria, yet in a certain number the symptoms of a profound inflammatory affection of the kidney are sufficiently pronounced to warrant the designation "acute nephritis." They are not, however, so numerous as those falling under the head of "simple albuminuria." If we put the two classes together as simply an expression in different degree of the same diseased action, the percentage of cases shewing renal affection in this series of 10,983 attacks comes out at 11·9.

The symptoms of onset in the majority of cases are sudden and pronounced, comprising headache, vomiting, sometimes a rigor, drowsiness, sudden elevation of temperature to 103° or 104° F., the appearance of blood and albumin in the urine, and a greater or less degree of suppression. The period of suppression corresponds usually with the febrile stage, and is seldom at its height until the third or fourth day, by which time the excretion may have fallen to three or four ounces, often with frequent desire to pass water. The skin is hot and dry, the pulse tense and excitable, the respiration rapid, the tongue dry, and by this time there is usually evidence of slight anasarca, best seen in the face, loins, hands, and feet. The febrile stage usually lasts from three to six days, and the temperature is very variable, often fluctuating between 97° and 102° or 104° F. several times during this period. It is hardly ever sustained for twenty-four hours at a stretch, but is of a strikingly "spiked" character when charted. The pulse, which has been variable both in rhythm and strength, not infrequently becomes preternaturally slow towards the end of the week, by which time the urine is passed in greater quantity. In a considerable proportion of cases the onset is much more gradual; the febrile signs, if present at all, being preceded by the appearance and gradual increase of albuminuria for several days. In these cases the condition does not at

any time look so alarming, but the prognosis is less favourable, and when recovery ensues, it is usually longer deferred.

Hæmaturia in some degree is constant, but anasarca to any extent is rare. The nephritis is often associated with adenitis, and not infrequently with rheumatism, which usually precedes it. Acute nephritis, like simple albuminuria, most frequently arises during the course of the third week. In a small number of cases it appears as late as the fourth week. It is most frequent in cold, damp, or "muggy" weather. All ages are liable to it, but it is less frequent after puberty. Sex seems to be without influence up to fifteen years, but at a later age males are more liable. Nephritis is as common after mild attacks of undoubted scarlet fever as after severe ones.

Recovery in the large proportion of cases is complete, and the albuminuria disappears in a few weeks. Occasionally, it is true, a slight degree of albuminuria will persist after several months' treatment, and a few of these patients, no doubt, become the subjects of chronic nephritis. But this, I am sure, is very exceptional in cases which have been properly treated from the outset. There is, I think, an undue tendency on the part of some physicians to ascribe the origin of a nephritis developing late in life to an attack of scarlatina many years previously. Scarlatinal nephritis is but rarely directly fatal, but when it is, death is almost invariably due to the advent of one of the three following conditions:—uræmia, suppurative inflammations, or acute pulmonary œdema. Of these the last is by far the most dangerous to life.

Secondary Tonsillitis.—This occurs much more often in adults and in older children, females being especially liable. A predisposition, moreover, is seen in connexion with the rheumatic diathesis, and in persons who are normally subject to throat affections. Although secondary tonsillitis in adults usually proves a mild disorder, in young children convalescence is liable to be complicated by the occurrence of a septic form of tonsillitis, attended with ulceration and much gland-swelling, which may be very severe and even fatal. Should this supervene during the pyrexial stage of scarlet fever there is little to distinguish the condition from an ordinary septic attack.

Ulcerative Stomatitis varies enormously in the severity of its manifestations. It most frequently begins as a simple sponginess of the gum, often in connexion with a carious tooth. Ulceration then appears at its free border, with a tendency to bleed on being touched. The diseased action next tends to spread laterally, and affects either the adjacent border of the tongue or the mucous surface of the cheek or lip. The disease may stop at this point, and remain limited to the appearance of a few shallow ulcers with an angry-looking margin and a greyish floor, in conjunction with the spongy ulcerated condition of the gum before referred to. Such cases are invariably attended with a moist and somewhat brownish coating to the tongue, a certain degree of salivation with enlargement of the submaxillary lymphatics, and a distinctive fetor of the breath. They do not usually present any rise of temperature or serious

constitutional disturbance. In other cases, however, things are very different. The ulceration of the gums rapidly spreads and assumes a necrotic form; the teeth become loose or fall out; the ulcers on the tongue, lip, and cheek take on a fungating character, or actual sloughs may appear in the latter situation, and eventually, if the case be left to itself, involve the whole thickness of the cheek. A black incrustation forms on the teeth, and the temperature may be raised several degrees with signs of profound constitutional depression. Cases of this degree of severity, deserving the name *noma*, are of rare occurrence nowadays, in London at any rate, and if taken early may be cured by energetic treatment.

Ulcerative stomatitis complicating scarlet fever is a disease of young children, being virtually unknown after the age of puberty. It shews no special relation to either sex or season, but is most common in strumous subjects, and in those who are suffering from, or who have recently had, measles. There is a distinct disposition for the diseased mucous membrane to become infected with diphtheria; I have seen this complication supervene in three cases of ulcerative stomatitis arising in the ordinary manner, and ultimately prove fatal by involvement of the larynx. This, however, was before the days of antitoxin. The affection is eminently contagious.

Bronchopneumonia.—This rarely occurs except as a late development of a septic attack. In some instances it is apparently set up by the passage of food and offensive secretions into the bronchial tubes; the normal mechanism concerned in guarding the laryngeal orifice having failed as the result of extension of the swelling and destructive ulceration from the contiguous faucial structures. In cases where the ulceration is not sufficiently extensive to interfere seriously with the mechanism of deglutition, the bronchopneumonia would appear to be but an additional manifestation of a general septic infection. The supervention of bronchopneumonia exerts a very prejudicial effect on the case. Dyspnœa and cyanosis become more pronounced, with corresponding depression of the pulse. The temperature is sustained, and the attack usually soon proves fatal.

Relapse.—A true relapse not infrequently occurs in scarlet fever, a state in which all the characteristic features of the disease are simply repeated in a person who has recently passed through one attack. As a rule, the severity of the relapse is in inverse ratio to that of the primary affection. Few relapses are fatal, though they are occasionally severe. The relapse may occur at any stage of the disease after the middle of the second week. Any attempt to draw a distinction between a relapse and a second attack is purely arbitrary. A true relapse would imply that the immunity conferred by the original attack is not sufficiently prolonged to protect a person from re-infection by the morbific agent which is still present in his own person. Relapses are said to be more common in hospital patients than in those treated at home, and as the infection in the air of a fever ward is constantly being renewed by the admission of fresh cases, it is held that a person whose immunity is short-lived is, consequently,

far more likely to fall a victim to the disease again. According to this view the relapse should more properly be called a "second attack." Amongst 10,983 cases of scarlet fever under my care during the years 1895-1904, a true relapse or second attack occurred in 1·1 per cent. In one instance a young woman had three definite attacks of scarlet fever within a period of three months; in the last of these she died. If a person succeed in throwing off the infection, and have passed out of his infected environment safely, he very rarely falls a victim to the disease again within the next ten or fifteen years, but a second attack after a long interval is by no means uncommon.

In addition to the more common affections detailed above, convalescence from scarlet fever is liable to be complicated by various minor ailments, which, however, may not be directly ascribable to the action of the specific poison. Of these, eczema, impetigo, purpura, boils, and ophthalmia are, perhaps, the most frequent. It should also be remembered that scarlet fever convalescents are very prone to contract any other infective disease to which they may be exposed, especially diphtheria, chicken-pox, and measles (see p. 845).

Post-Scarlatinal Diphtheria.—As to the factors concerned in the development of this, which in pre-antitoxin days proved the gravest complication to which the scarlet fever convalescent was liable, considerable uncertainty prevails. Though any stage of the scarlatinal attack may be complicated by the appearance of diphtheria, it is during convalescence that the large majority of cases arise. It occurs more frequently in hospital-treated patients than in those who remain at home, at any rate among the better classes. This suggests that its incidence is dependent upon conditions which are to a great extent special to hospital life. Now, experience shews that its frequency varies in different hospitals, in different wards, and at different times in the same hospital. Many suggestions have been offered to explain its appearance.

The presence in a scarlet fever ward of a previous case of diphtheria which, owing to its extreme mildness may have entirely escaped detection, must certainly be admitted as the most likely source of infection. This is more particularly true of nasal diphtheria. It is remarkable that a recognised case of faucial or laryngeal diphtheria seems to but rarely give rise to other cases in a well-ventilated scarlet fever ward, provided there is no overcrowding, and due care be taken in its management. The possibility of the disease being derived from the nurse, in consequence of her harbouring diphtheria bacilli in her own throat, or of mediate infection through the agency of linen, books, toys, and so forth. or the clothing or hands of an attendant whose mucous membranes are above suspicion, must never be overlooked. The circumstances connected with the appearance of post-scarlatinal diphtheria in certain hospitals frequently suggest that a predisposition is engendered by the operation of some more general and widespread influence, such as an atmospheric or soil condition. Cases of post-scarlatinal diphtheria are frequently

observed to arise in groups of two, three, or more, almost simultaneously or in close succession, in different wards of a large hospital, wards which are not only widely separated, but which may have no administrative factor in common, with the exception of the food-supplies which can be clearly absolved. Such outbreaks have not infrequently arisen in seasons characterised by a high degree of atmospheric humidity, dependent upon previous rainfall and consequent dampness of soil. The incidence of the disease appears to be greatest in wards surrounded with grass or other vegetation growing in a clay soil; indeed, the moisture-retaining character of the actual surface would seem to be of greater importance than the subsoil drainage, whether natural or artificial, though it must not be forgotten that in certain exceptional instances a connexion has been conclusively established between outbreaks of diphtheria and defective drainage. I have, however, come across cases in which it was possible to eliminate all such influences, in so far as they are capable of elimination. Statistics, moreover, go to prove that the incidence of the affection bears no relation to the proximity of a diphtheria ward. At one hospital which has enjoyed a comparative immunity from post-scarlatinal diphtheria, its incidence has been more than twice as frequent in wooden huts, deficient in floor-space per bed, than in brick-built wards with an ample provision: and its appearance has been strikingly shewn to follow in the wake of even temporary overcrowding of wards in other respects satisfactory. In the treatment of scarlet fever it is most necessary that the heating appliances in a ward should be capable of maintaining the air at a satisfactory degree of warmth and dryness, and at the same time permit of ample direct ventilation. The floor-space per bed should on no account be reduced below 144 square feet, and the airing-court surrounding the ward should have a gravel surface, or better still, perhaps, be laid with tar-paving. Were these points insisted upon in the construction of all fever hospitals, there is little doubt that the incidence of post-scarlatinal diphtheria would be considerably reduced, assuming due care to be exercised in respect to their administration.

The incidence of post-scarlatinal diphtheria amongst 36,230 cases of scarlet fever admitted into certain of the Asylums Board Hospitals during the years 1890-94 was 1·7 per cent. Of these, 54·4 per cent were fatal; but this was before antitoxin was available. In exceptional cases its incidence in a single hospital has risen to over 4 per cent of the admissions.

There is nothing, either clinically or bacteriologically, to distinguish post-scarlatinal diphtheria from the independent disease, except in respect to its unduly high mortality. While the mortality in the series under consideration was 54·4 per cent, that of the diphtheria admissions in the same period, numbering 10,777 cases, was 29·6 per cent. This excessive mortality is in great part because more than half of the attacks occurred in children under five years of age, who, in primary diphtheria without antitoxin, died at the rate of 50 per cent in the public fever hospitals of London. Moreover, having regard to the fact that in something like 75 per cent of these children the disease assumed the laryngeal form, it may

Chart 7.

Showing time of incidence of
POST-SCARLATINAL DIPHTHERIA *at*
different stages of convalescence
from Scarlet Fever.
Compiled from 1503 Cases.

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be confidently stated that the excessive mortality in post-scarlatinal diphtheria is mainly due to a special tendency of the disease to affect the respiratory passages. The results following tracheotomy, again, are not so favourable as when the operation is performed in cases of independent diphtheria.

The following table deals with the time of incidence of the diphtheritic complication in 1503 cases :—

TABLE V.—Time of Onset in 1503 cases of Post-Scarlatinal Diphtheria.

Week.	Under Five Years.	Over Five Years.	Total.	Percentage of Total Cases.
1	19	8	27	1·79
2	61	34	95	6·32
3	110	78	188	12·50
4	186	108	294	19·56
5	126	73	199	13·24
6	93	44	137	9·11
7	85	48	133	8·84
8	77	51	128	8·51
9	54	35	89	5·92
10	30	22	52	3·45
11	27	10	37	2·46
12	26	17	43	2·86
Later than 12th	60	21	81	5·38
Total	954	549	1503	100·

The variation in the time of incidence is best seen if the above numbers are shewn in the form of a chart (No. 7), and, since the rise and fall of the curve is both regular and progressive, it may be fairly taken as an expression of the varying susceptibility to the disorder at different periods of the scarlatinal attack. This tends to shew in the most striking manner that susceptibility is at its maximum during the course of the fourth week.

If it be permissible to argue from results which have recently been attained, the prospects of success in the field of serum therapeutics are certainly more encouraging.

Treatment.—It must be confessed that all attempts to control the course of scarlet fever by means of drugs have hitherto been unsuccessful. Many and various have been the drugs for which an abortive action has been claimed; usually, it would seem, upon the strength of a few cases which have recovered after their administration. These drugs have been mainly of the antiseptic class, and, when their action has been continuously tried on a large series of cases, their superiority over ordinary methods of treatment has been in no way apparent.

1. *Serumtherapy.*—Quite apart from any question as to their specificity, the important part which of late has been ascribed to streptococci in

connexion with those grave developments of a septic nature which characterise the majority of severe cases of scarlet fever, and which appear to be mainly responsible for the gravity of the patient's condition, not unnaturally stimulated the hope that a serum prepared from these micro-organisms might be capable of exercising a curative influence on the course of the disease. Antistreptococcic serum, therefore, though originally prepared by Marmorek for the treatment of erysipelas, appeared to meet the want, and it received an extensive trial in the septic form of scarlet fever in addition to other varieties of streptococcic infection. The results, however, in so far as scarlet fever was concerned, proved wholly disappointing, though Baginski formed a favourable opinion of it. It was urged by Aronson that the frequent failure of antistreptococcic serum might be explained by the assumption that the streptococci from which the serum had been prepared might be of a different strain from those whose operations in the body it was desired to counteract. In accordance with this assumption, and in order to reduce, as far as possible, the chances of failure, Aronson prepared a serum by immunising a horse with a number of different strains of streptococci derived from various sources. The same principle was followed out by Tavel, and subsequently by many others, and an antistreptococcic serum has actually been produced from the use of no less than forty different strains of streptococci. The results obtained with polyvalent serum in the treatment of scarlet fever, though falling short of expectations, have on the whole proved somewhat more successful.

A departure in the right direction was made by Moser of Vienna, who, in the year 1900, prepared a serum from streptococci exclusively derived from the blood of fatal cases of scarlet fever, and claimed extremely good results; the success of this serum was also attested by Escherich. The same principle has been followed by Besredka, Bujwid, Dowson, and others with more or less success. By the courtesy of Dr. Besredka, I have been enabled to try his serum on forty-four cases of septic scarlet fever. The serum, prepared at the Institut Pasteur, may justly be described as a "polyvalent antiscarlatinal serum," seeing that more than twenty separate strains of streptococci isolated from cases of scarlet fever were employed in its preparation. The serum was only given in grave attacks, attacks, indeed, which my experience led me to think would be likely to prove fatal under ordinary methods of treatment. The actual mortality amongst these forty-four attacks was 36·3 per cent, a result which I regard as distinctly encouraging. In some, the administration of serum appeared to bring about a rapid and striking improvement. In others, on the contrary, it did not seem to have any effect, but I was quite unable to recognise any special indications by means of which one might form an opinion as to its probable success or failure. It would seem, however, that early and sufficient dosage are of paramount importance. The mortality amongst seventeen cases in which the treatment was commenced by the fourth day or earlier was 23·5 per cent; that amongst seventeen cases treated on the fifth to the seventh day was

35·2 per cent; while that amongst ten cases treated on the eighth to the tenth day was 50 per cent. The amount of serum given at each injection was 50 c.c., repeated daily, when necessary; the average number of injections being four.

In view of the work of Drs. Klein and Mervyn Gordon, it is interesting to note that Palmirski and Zebrowski made an extensive trial of a serum stated to have been prepared exclusively from *Streptococcus conglomeratus* which they succeeded in isolating after death in seventeen fatal cases of scarlet fever. They used the serum in about one thousand cases of infantile scarlatina in the Children's Hospital at Warsaw, but they only record its action in a hundred and thirty-three severe attacks. They found that in mild cases it acted like a charm; in septic attacks it acted well, though more slowly; but they are doubtful whether, with the exception of nephritis, it had any protective influence against the more common complications of scarlet fever. All cases in which *Streptococcus conglomeratus* was detected in the blood during life proved fatal and were in no way influenced by the serum. If the criteria adopted by these observers for the identification of their organism as the *Streptococcus conglomeratus* be above criticism, the striking and immediate effect of the serum which they report on the mild cases has a bearing of no small importance on the claims advanced by Drs. Klein and Gordon in favour of the specific relation of that organism to scarlet fever.

In view of the comparatively large doses of antistreptococcic serum necessary (25-50 c.c.), and the desirability of repeating the injection on several successive days if the serum appear to be doing good, as evidenced by an almost immediate, though usually temporary, fall of temperature, it is always well to select a different site for each injection. The liability to subsequent suppuration at the seat of injection is much greater than when antitoxin is similarly employed in cases of diphtheria. Even greater care, if possible, should be taken to render the operation aseptic, though it is by no means improbable that the greater frequency of abscesses in this class of case is actually determined by streptococci already present in the circulation.

2. *General Treatment.*—The patient should be placed in a room which can be freely ventilated, and, at the same time, adequately warmed. This should be effected, if possible, by means of an open fire, the ingress of fresh air being provided for by keeping the top sashes of the windows more or less open both day and night to an extent proportionate to the state of the weather. The air of the room should be kept as dry as possible, and maintained at a temperature of from 56° to 60° F. A warm temperature is of more importance during convalescence than it is in the acute stage of the disease. A horse-hair mattress, preferably supported on a chain or wire-wove under-mattress, is the best; and the bed-clothes should be light but warm. During the febrile stage linen should be worn next the skin; but when the temperature has fallen, flannel should be substituted, and either it or a woollen vest be worn throughout the period of convalescence. The hygiene of the sick-room, though

important, does not call for special remark, but should be conducted on rational principles.

So long as fever is present, the surface of the body, at any rate down to the hips, should be washed daily with soap and water, and the action of the skin encouraged by an occasional tepid sponging, due care being taken, of course, to avoid unnecessary exposure of the surface. It is well to "tepid-sponge" the patient every evening as a matter of routine. By this means not only is the tension of the skin lessened and the temperature somewhat reduced, but restlessness is diminished and quiet sleep promoted.

A febrifuge mixture, containing either bitartrate, nitrate, or chlorate of potash, and acetate of ammonia, combined with spirits of nitrous ether and a little syrup of orange or lemon peel, may be given every few hours with advantage. A lemonade, composed of lemon juice, bitartrate and chlorate of potash (āā gr. iii.-v. ad ℥j.) and soda water, sweetened with sugar, forms a refreshing and useful beverage. The bowels should be encouraged to act daily by means of some mild laxative; for this purpose nothing is better than compound liquorice powder, or the confections of senna and sulphur. In young children an occasional glycerin enema may be sufficient, and, in patients who are getting up, a glass of cold water taken first thing in the morning may be all that is required. A tonic is often indicated during convalescence, preferably one containing iron, in view of the frequent presence of some degree of post-scarlatinal anæmia. The urine should be tested daily for albumin, especially during the second and third weeks. In order to diminish the risk of renal complication, and to facilitate peeling, frequent warm baths should be ordered, starting from the day on which the temperature has fallen to normal; if possible, they should be given daily.

There is no reason why the subjects of mild scarlet fever should not be allowed to get up at the end of ten days or a fortnight, provided no complication has arisen, and due care be taken to avoid chill or undue exertion. Young children, however, may with advantage be kept in bed for three weeks after the appearance of the rash, as they are prone to develop some complication during this period. If the weather be dry, and the patient suitably clad, a moderate amount of outdoor exercise is of distinct benefit. In these circumstances he may be allowed to go out after having been up for two or three days. If the weather be damp, however, and the patient foolish enough to sit about, the practice is then by no means devoid of the risk of renal or glandular complication. For this reason young children, during the early weeks of convalescence, should not be allowed to go out of doors unattended.

When the period of isolation has expired, which, even in the absence of any discharge from the nose or ears, should not be less than five or six weeks, a short residence in the country, if possible at the seaside, will be of permanent value after a severe attack.

The diet during the febrile stage should mainly consist of milk and beaten-up eggs, but the addition of a little soup, beef-tea, mutton- or

chicken-broth, and calves'-foot jelly, forms a welcome variety, and will do no harm. As soon as the temperature has fallen a more solid diet is permissible; and bread soaked in milk, custard, milk puddings, lightly-boiled eggs, and thin bread and butter, devoid of crust, may be added to the dietary, provided the state of the throat permits of their being swallowed without discomfort. In the course of two or three days the diet may be extended so as to include fish, poultry, or meat.

On purely theoretical grounds it has been contended that nitrogenous food should be withheld during early convalescence from scarlet fever, in order to avoid throwing too much stress upon the kidneys. I am able, however, to assert with considerable confidence that no such risk is found in practice, and that patients will suffer no harm whatever if put on such a dietary as I have described above. There is, moreover, no evidence that nephritis has ever been induced by the administration of a diet containing a moderate amount of nitrogenous food. The desire of the patient himself for solid food is the best criterion of its advisability, and it may be given with confidence as soon as he feels able to swallow it without discomfort. Ripe and succulent fruit may be given at all times throughout the illness. It is not only refreshing, but wholesome.

When there is much swelling or ulceration of the faucial structures, especially if attended with tenderness and infiltration of the submaxillary lymphatics, it may be extremely difficult to prevail upon the patient to take his nourishment; and the same thing is frequently true in cases of the toxic type, the patient being usually restless and refractory, if not actively delirious. In such cases the food should be administered in small quantities, and in as concentrated a form as possible, reliance being then mainly placed upon some of the various meat-essences, though freshly prepared raw beef juice is probably more valuable. These, too, are the only cases in which stimulants are necessary, and even here their use should be cautiously regulated. To a child of five years of age it will be rarely necessary to give brandy in larger quantity than at the rate of half a teaspoonful every hour. In prolonged cases of the septic type, meat-juice combined with alcohol in a palatable form will be useful. Deglutition in some cases becomes practically impossible; it may then be necessary to pass a nasal tube, or feed entirely by the rectum.

3. *Symptomatic Treatment.*—The local treatment of the throat in scarlet fever is of the first importance. In mild attacks, and in those of the toxic variety, nothing more is necessary than to irrigate the fauces every few hours with some mild antiseptic solution, such as boracic acid, bicarbonate of soda, sulphurous acid, or Condy's fluid, applied by means of either a syringe or spray. In adults the throat may be gargled. Local discomfort may be lessened by frequently sucking small pieces of ice, but in some persons more relief is obtained when the fluid nourishment is taken as hot as it can be borne. Hot fomentations or a linseed-meal poultice, properly made and evenly applied, should be placed round the throat in all cases in which the glands are enlarged and tender. They not only considerably diminish the pain on swallowing, but also appear

to favour resolution; moreover, if suppuration threaten, the process seems to be hastened by their application.

In septic cases, however, in which the tonsils threaten to ulcerate, or are coated with exudation, more vigorous methods are called for. Here it is necessary to bring the diseased surface into as healthy a condition as possible by means of some more powerful antiseptic solution, frequently used, and at the same time to cleanse the naso-faucial passages from offensive accumulations. For this purpose nothing is better, if, indeed, so good, as an acid solution of chlorate of potash containing a large amount of free chlorine. The solution is prepared by pouring strong hydrochloric acid upon powdered chlorate of potash in a large stoppered bottle, and afterwards shaking up with water. The best proportions are 5 minims of the strong acid to 9 grains of the salt, made up to an ounce with water. The resulting solution is of a greenish-yellow colour, and smells strongly of chlorine. This is used with an equal volume of either hot or ice-cold water, and the fauces should be thoroughly syringed out every two or three hours according to the severity of the local affection, the syringe best adapted for the purpose being what is known as a four-ounce rubber enema bottle, fitted with a vulcanite nozzle. It is best to employ two syringes at each operation, one being allowed to fill itself in a basin containing about a pint of the solution while the other one is being used. By the time the latter is empty the other will be ready charged, and there is consequently no loss of time. This latter point is of considerable importance to the patient, as the process is by no means pleasant. This is far the best method of dealing with a septic throat, as the solution, which is strongly antiseptic and astringent, is injected in such a manner as to clear the faucial passage of any offensive secretion. No amount of gargling, spraying, or swabbing can compare with it in point of efficacy, even if the parts be reached. The patient's head should be held over a basin and the mouth kept open. The solution may be injected with some force, as no harm can be done by a stream of fluid, but sufficient time must be allowed for the patient to get a breath between each squeeze of the syringe. The relief obtained is very great, and even young children, after a short experience, will often willingly submit to its repetition in view of the comfort which follows. By frequently irrigating the diseased surface in this manner the local multiplication of pyogenetic and putrefactive organisms is to a great extent held in check, and, consequently, the chance of an extension of the ulceration is considerably lessened.

Having regard to the tendency which exists for the morbid process to involve the naso-pharynx also, as evidenced by the frequent occurrences of rhinorrhœa, it is wise to irrigate the nasal passages as well. If a solution of chlorine be employed for the purpose, this should be used in more diluted form, or one of boric acid, Condy's fluid, or salt may be substituted, as being less irritating. If a syringe be used for washing out the nasal passages, the fluid should be injected very gently, since there is a risk of driving inflammatory products up the Eustachian tube,

and setting up inflammation of the middle ear if undue force be employed. In unskilled hands a nasal douche is best adapted for the purpose.

Dr. A. K. Gordon, of the Monsall Fever Hospital, is of opinion that the daily use of a douche to the throat and nose in the acute stage of scarlet fever helps to prevent otorrhœa, and he recommends the employment of sterilised water for this purpose. I am not convinced of the necessity for this in mild attacks when the nasal passages are free and unobstructed, but in young children whose naso-pharynx is blocked with adenoids, I believe the practice to be of prophylactic value. Persistent and intractable rhinorrhœa is in most cases due to the presence of adenoids, and their removal, even in the early convalescent stage, is followed by the best results.

If the cellular tissue in the submaxillary or cervical region become the seat of brawny infiltration, it is better at once to make several free incisions into the part affected, rather than to wait for the appearance of definite suppuration. This not only relieves pain and tension, but at the same time provides an escape for the pent-up inflammatory products. In such cases the presence of actual suppuration is often very difficult to determine; indeed it may be absent altogether. Frequently, however, an abscess forms under the sterno-mastoid or beneath the cervical fascia. This should be opened at once and a drainage-tube inserted. Afterwards, hot fomentations of boracic or carbolic acid should be applied, and changed frequently.

Insomnia, restlessness, and delirium are usually associated with a high temperature. For their relief recourse should be had, in the first place, to cold, or tepid, sponging. If this fail, opium, sulphonal, trional, or chloralamide may be tried in doses proportionate to the patient's age. Sponging is frequently beneficial, but should be used with caution after the middle of the second week, when, if albuminuria be present, its employment is contra-indicated.

The treatment of hyperpyrexia is usually unsatisfactory, and most cases are ultimately fatal. A cold pack should be tried, and its effect carefully watched. Of all drugs, antifebrin, in two to five grain doses, is the best. The dose may be repeated in four hours if the temperature has again risen. No other drug appears to be of equal service, and the combination of antifebrin with the wet pack is sometimes of great value. The use of the graduated bath in scarlatinal hyperpyrexia is recommended by some physicians, but in my hands the remedy has not proved very satisfactory. The temperature of the water at starting should be about 90° F., and this should be rapidly reduced until the body-heat has fallen to about 101°.

Diarrhœa, appearing early in the illness, had better be left to itself; but when it complicates the late stage of a severe attack, it must not be neglected. In such cases Dover's powder is often useful, especially when combined with equal parts of bismuth subnitrate and salicylate of soda. A powder containing two grains of each may be given to a child of five, and can be repeated in four to six hours if necessary.

The treatment of the recognised complications of scarlet fever is important. Some years ago, while testing upon a series of cases the value of decoction of cinnamon—for which an abortive action had been claimed by Dr. Carne Ross, in cases coming under treatment at a sufficiently early date—I was surprised to find a considerable reduction in the incidence of some of the more common complications of the disease. Indeed, in a series of 200 consecutive cases which were put under this treatment within twenty-four hours of the appearance of the rash, the incidence of adenitis, rheumatism, nephritis, and albuminuria was found to be about 50 per cent below the average. The general death-rate, however, shewed no reduction.

Otitis.—The earache, which in some degree is very often present at an early stage, should be treated by gently irrigating the affected ear with water as hot as it can be borne. After this a few minims of laudanum or glycerin of carbolic acid, previously warmed, may be dropped into the canal, and a hot fomentation of opium or belladonna applied externally. The instillation of a few drops of a 5 per cent solution of cocaine in liquor atropinæ will sometimes quickly give relief when the former remedies have failed. Now, although from a surgical point of view it may be desirable to incise the membrana tympani directly the drum shews any sign of bulging, in the young children who are almost invariably the subjects of the acute scarlatinal affection the external canal is usually so tender, and its calibre so small, that not only is the passage of the speculum extremely painful, but a satisfactory inspection is very difficult. If the membrane rupture spontaneously (which it usually does in a short time), it is doubtful whether any harm results from neglect of this procedure provided the after-treatment be carefully carried out. In many instances the early appearance of the discharge will anticipate surgical interference; indeed, more often than not, it is the first sign of the affection. When otorrhœa is once established it is of paramount importance to keep the middle ear as aseptic as possible. With this object the ear should be carefully syringed every three or four hours with some antiseptic solution; the canal should then be dried, and a small piece of cyanide or alembroth wool, sprinkled with iodoform, inserted in the meatus. A good lotion to employ is a saturated solution of boracic acid or one containing a mixture of equal parts of glycerin of carbolic acid and glycerin of borax, in the proportion of half a drachm of each to the ounce of water. If, after a few weeks' treatment, the discharge do not markedly diminish, it is advisable to change the solution for some other possessing more astringent properties. A good substitute is a lotion of carbolic acid, 1 in 40, containing also two grains to the ounce of either sulphate of zinc or sulphate of copper, varied occasionally by the use of a weak solution of cyllin. If the perforation in the drum be large, a few grains of iodoform may be blown up the meatus after syringing, more especially if the discharge be very offensive. At a later stage a few drops of dilute rectified spirit can be instilled into the ear occasionally, the strength being gradually increased.

The occurrence of pain and tenderness, accompanied by redness and

swelling over the mastoid bone, are indicative of the presence of a mastoid abscess. This is usually attended with pyrexia of some degree. For its relief a vertical incision should be made right down to the bone, immediately behind the ear, taking care to divide the periosteum. In this way a sub-periosteal collection may be relieved, though usually the amount of pus is small and may easily escape detection. The bone always feels rough to the probe, though it may be distinctly carious, in which case pus is usually present in the mastoid antrum. In these circumstances anthrectomy should be performed, any granulation-tissue found in the cavity removed, and free drainage provided for the middle ear by at the same time enlarging both the communication between the antrum and tympanic attic and the perforation in the membrana tympani. Occasionally, the only sign of mastoid suppuration is the persistence of otorrhœa with irregular pyrexia, or the sudden occurrence of facial paralysis.

In view of the serious risk of infection spreading to the lateral sinus, brain, or meninges, every case in which suppuration within the mastoid bone is suspected should be at once submitted to operation, and, indeed, it is a question whether it is not wiser, having regard to the risk of involvement of the mastoid cells, to provide free drainage by opening the mastoid antrum in all cases in which an otorrhœa has persisted for several months, and proved refractory to ordinary treatment. This is especially important in cases where the discharge is distinctly offensive, or when the presence either of granulations or carious bone can be detected in the middle ear. Such cases nearly always require the complete mastoid operation. By this means not only will ultimate danger to life through extension of the disease be averted, but cure is likely to be more rapid, and with less chance of complete loss of hearing. For information as to the details of the particular operation which may be indicated in different cases, a work dealing with the surgery of the mastoid region should be consulted.[1]

Adenitis.—This affection, when recognised at an early stage, is best treated by the application of a linseed-meal poultice, by which means resolution seems to be favoured. If suppuration occur the abscess should be at once opened and a drainage-tube inserted. Warm dressings of boracic or carbolic acid should then be applied, and frequently changed.

Rheumatism.—In most cases the local application of opium or chloroform and belladonna liniment will be sufficient. The painful joints should be surrounded with warm cotton-wool, and a flannel bandage applied, while the affected limbs are supported in as comfortable a position as possible by means of pillows. If the joint affection be severe, and in those rare instances in which the cardiac structures become involved, the free use of the salicylates will be attended with the best

[1] An excellent description of the operations referred to, and of that necessary for the relief of septic thrombosis of the lateral sinus, will be found in Sir W. MacEwen's work on the *Pyogenic Diseases of the Brain and Spinal Cord*, published by J. Maclehose and Sons, Glasgow.

results, nor is there any reason to believe that their administration ever affects the kidneys injuriously. If, however, one or more of the joints remain swollen and tender for any length of time, and the temperature show no reduction under full doses of salicylate of soda or aspirin, a little fluid should be withdrawn from the joint, by means of an aseptic hypodermic syringe, and examined. If it be purulent the joint must be opened, under strict aseptic conditions. A small incision should be made into it on each side, and as the fluid escapes the joint should be irrigated, even to the point of distension, with a 1 in 2000 solution of corrosive sublimate. This should be allowed to escape, and the openings closed by means of a small piece of antiseptic gauze soaked in collodion. Firm but elastic pressure should then be exerted upon the joint by means of a bandage tightly applied over several layers of cyanide wool, and the limb placed upon a splint. In many cases I have found this treatment entirely successful, no reaccumulation of pus having ensued. Gentle passive movement was allowed at the end of two or three weeks, and a sound joint was the result. This sub-pyæmic condition seems invariably to have supervened upon an affection which, though originally, as far as could be seen, rheumatic, did not prove amenable to the action of the salicylates.

Nephritis and Albuminuria.—When the renal inflammation takes an acute form, as evidenced by the severity of the constitutional disturbance and the degree of urinary suppression, the treatment should be mainly directed towards the encouragement of a free action of the other excretories —the skin and bowels—and towards lowering the arterial blood-pressure. With these objects in view a hot air or steam bath should be given daily. Free perspiration may be assisted if necessary by means of frequent draughts of cold water. Some purgative also, calculated to produce copious watery evacuations, should be given in full doses; and for this purpose, either sulphate of magnesia or soda, or the compound powders of jalap, elaterium, or scammony, may be employed. The bowels should be kept loose by repeating the dose, if necessary daily. Wet-cupping the loins to the extent of several ounces may be of service in cases in which the suppression is nearly complete, but the employment of dry-cupping, or the application of poultices to the loins, is practically useless. The hot air or steam bath is especially indicated when the skin acts badly, and when there is obvious anasarca; and in these cases a diaphoretic mixture containing acetate of ammonium, nitrate of potash, and spirits of nitrous ether may be given every three or four hours.

The diet should consist of milk only, preferably diluted with soda-, lime-, or barley-water; and lemonade may be given freely. The vomiting may prove very troublesome, in which case the milk should be peptonised, and administered in small quantities. Though drugs are not usually of much service, the retching may sometimes be controlled by drop doses of tincture of iodine given hourly in a teaspoonful of water.

Most cases of scarlatinal nephritis will progress favourably under the above treatment. The re-establishment of the urinary excretion, attended by a fall in the blood-pressure, the disappearance of œdema,

and a normal temperature, are the signs to be looked for. In these circumstances, if the vomiting have ceased, the diet may be gradually extended so as to include bread and butter, farinaceous puddings, and white fish. Now is the time at which iron in some form is most useful, and none is better than the tincture of the perchloride given in 10-15 minim doses three or four times in the twenty-four hours.

When the case has so far progressed that no signs of nephritis remain (other than slight albuminuria, and a certain degree of anæmia), the inclusion of a couple of boiled eggs in the dietary will be beneficial. This will help to replace the albumin which is constantly being passed in the urine; and under the influence of an appreciable amount of coagulated proteid and the free administration of iron a patient will usually put on flesh and gain colour with greater rapidity. If at any time uræmia threaten, as shewn by drowsiness, headache, vomiting, and (more important still) the slightest suspicion of muscular twitching, the most energetic measures are called for at once. Then, one or two drops of croton oil, floated in a teaspoonful of milk, should be given immediately; the body, well covered with blankets, should be at once placed in a hot air or steam bath, and $\frac{1}{6}$ to $\frac{1}{4}$ grain of pilocarpine injected subcutaneously. If the arterial pressure be high, $\frac{1}{100}$ grain of nitroglycerin may be given; or better still, the patient should be bled, the amount of blood being regulated by the effect produced upon the pulse. The case must be carefully watched, and if the breathing become embarrassed, through spasm of the glottis or respiratory muscles, chloroform should be administered forthwith. A few whiffs will frequently relieve the respiratory spasm and consequent cyanosis. It should be repeated as often as may be required. By its use not only is an immediate danger removed, but time is given for the other remedies to act. Most cases of uræmic convulsions can be saved by energetic and judicious treatment.

The onset of acute pulmonary œdema is, in my experience, invariably fatal. Venesection would appear to hold out the best prospect, and digitalis should always be tried with the object of contracting the pulmonary capillaries. During the acute stage of nephritis, and for a week or two afterwards, the patient should be kept between blankets, nor should he be allowed, in any circumstances, to get up for at least a month from the onset of the affection. He should in all cases be kept strictly confined to bed until the amount of albumin has fallen to a trace, and flannel should constantly be worn next the skin, not only throughout convalescence, but for several months afterwards.

If the patient has been getting up for a week or two, gentle out-of-door exercise may be allowed in *dry* weather. This, if the body be warmly clad, will be of distinct benefit, even though a trace of albumin remain. A few weeks' change at the seaside will in most cases complete recovery.

Persistent albuminuria, of more than three or four months' standing, probably always points to permanent impairment of at least some portion

of the renal tissue. In these cases residence in a warm, dry climate, and extreme care in respect to both habits and diet, are to be recommended.

Ulcerative Stomatitis.—In mild cases nothing more is required than to syringe out the mouth every few hours with a solution of chlorine, Condy's fluid, or corrosive sublimate, and to paint the affected surface occasionally with glycerin of borax or nitrate of silver. The teeth should be kept carefully cleansed, and any carious stumps removed. In those exceptionally severe cases which are known by the name of "Noma," the diseased and sloughing surface should without loss of time be scraped thoroughly with a curette, and fuming nitric acid afterwards freely applied. This operation may usually be done under cocaine, but in the worst class of case, or in those which have not come early under treatment, the disease may be so extensive that a general anæsthetic may be required. After operation the inside of the mouth should be brushed over with olive oil, and periodically syringed out with some antiseptic lotion. If after forty-eight hours the disease be seen to be extending at any point, the affected part should again be destroyed. Excision of the parts will rarely be required if the case be got under treatment sufficiently early.

Tonsillitis and Bronchopneumonia.—The treatment of these affections presents no special feature, and should be conducted on ordinary lines.

F. Foord Caiger.

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CHICKEN-POX

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SYNONYMS.—*Varicella, Variola crystallina, Crystalli*; Ger. *Wasserpocken, Varicellen, Windpocken, etc.*; Fr. *Varicelle*; Ital. *Varicella.*

A SPECIFIC infectious disease characterised by a vesicular eruption which usually appears in successive crops.

Chicken-pox was long confounded with small-pox, but since Fuller in 1730 and Heberden in 1767 differentiated the two diseases no authority of eminence, except Hebra, has affirmed their identity. The strongest points in support of their non-identity are that neither chicken-pox and small-pox nor chicken-pox and vaccinia are mutually protective, and that chicken-pox breeds true. Several instances have come under my observation of vaccinated children between three and six years of age who suffered from chicken-pox, contracting small-pox after a short residence in a small-pox ward; and I have vaccinated with success numbers of unvaccinated children suffering from chicken-pox.

Chicken-pox arises solely from contagion, by direct contact with the sick, by the air for a short distance, by third persons handling the sick, or by means of infected articles. Many investigators have tried to inoculate chicken-pox, but with the exception of Hessa and Steiner, who state that they have done so with success, all have failed. In my experience it is a highly contagious disease—its infectivity being nearly, if not quite, equal to that of small-pox. It prevails occasionally in epidemic form, but is mostly endemic. Its highest seasonal prevalence is perhaps in autumn. Insusceptibility to its contagium is not uncommon, and one attack usually protects for life. Second attacks have been recorded by Trousseau and others, but they are quite rare. A week or two only may elapse between the primary and second attacks. Such cases might, however, be more correctly termed relapses. Some German physicians have noted third attacks. I have not seen a second attack. It is a disease of children mostly, but it occurs not infrequently in adults, even old age not being exempt. I have seen seven cases in persons over thirty; one of

these was a woman aged seventy-one. The age of maximum incidence is from one to six years, but it often occurs in infants under twelve months. Both sexes are equally liable.

Morbid Anatomy.—The vesicle is formed by an exudation of serum raising a thin layer of horny epidermis. The serum, at first clear, in some cases a pale straw colour, becomes turbid later on owing to the presence of a few leucocytes, which are sometimes present in such large numbers that it becomes purulent. Unna, in his description of a conical chicken-pox lesion, says that it has a tent form, the lateral walls rising obliquely from a broad base towards the centre of the covering which is formed by a few stretched horny scales. Cellular partitions radiate downwards from the covering, contrasting with the small-pox lesion in which the partitions radiate from a central point on the floor of the pock. The cavity proper of the chicken-pock is limited below by the deeper strata of the prickle layer. In the middle line the cavity extends deeper, to the level of the papillæ, which, swollen and enlarged, and covered only with one or two layers of altered epithelium, project into the cavity. The acuteness which distinguishes the varicellous process is evident in the relatively large, slightly septate cavities, due to the rapid distension of a few liquefied cells. The thin covering and superficial position of the vesicle result from its rapid formation. Notwithstanding its appearance the vesicle is not unilocular.

Bacteriology.—Bareggi described an ovoid-shaped micrococcus in the white blood-corpuscles on the fifth day of the disease, by inoculating cultures of which he has communicated chicken-pox to children. Guttmann isolated white and yellow staphylococci, and a coccus which did not liquefy gelatin, and shewed a yellow growth, but none of these are pathogenetic. Rille affirms that micro-organisms are less numerous in the suppurating vesicles than in the others, and Pfeiffer describes protozoa as present in the vesicular fluid (Guinon). De Korté has found in the clear vesicular serum large numbers of unicellular elements—protozoa—which on a warm stage shewed amœboid movements. He regards these as the causal organisms of the disease.

Incubation-Period.—Of the older authorities some maintained it to be less than a week (four to six days), others a week to fourteen days; the most recent observations go to prove that it varies between the extremes of eleven and twenty-one days, fourteen days being admittedly the most common. I have not seen it less than thirteen or longer than seventeen days. If inoculated, the incubation-period is stated to be ten days. No cases of chicken-pox in utero have been recorded; but Hubbard records a case of a baby that manifested chicken-pox the day after its birth, when the characteristic vesicles appeared, followed next day by a second crop. The mother was not suffering from chicken-pox, but her six other children were. In this case, either the child contracted the disease in utero, or the incubation-period was one day.

Clinical Picture.—*Initial symptoms.*—In children these are usually absent, or are so slight that they escape notice, but not infrequently the

child is observed to be fretful for a few hours before the appearance of the eruption, and there may be slight rigors with rise of temperature to 99°–100° F., and some loss of appetite and perhaps vomiting. In rare cases the attack is ushered in by severe symptoms, such as delirium, convulsions, coma, with or without pyrexia. Thomas records a case with a temperature of 106° F., and an initial general erythema. Others have noted a scarlatiniform initial eruption a few hours before or on the day preceding the vesicular eruption. I have met with a case, a girl of seven years of age, shewing a bright red erythema with numerous urticarial wheals. The rash came out twenty-four hours before, persisted till shortly after the appearance of the characteristic chicken-pox eruption, and was unaccompanied by any symptoms of illness. In hæmorrhagic cases there is slight rise of temperature for two or three days before the eruption appears; repeated hæmatemesis and hæmorrhage from the bowel may occur, followed by collapse and subnormal temperature; hæmorrhages may appear in the skin. In adults it is not unusual to find initial symptoms of headache, backache, slight rigors and malaise, lasting for one, two, three, or more days before the appearance of the eruption, with or without rise of temperature.

Eruption.—In children, when initial symptoms are absent, the presence of the eruption first attracts attention. It may all appear at once, and will then probably not be abundant. But in a very large majority of the cases successive crops appear from day to day, usually on not more than four, five, or six successive days, sometimes on as many as ten, with perhaps one or two days intermitted; the second and third crops are often more abundant than the first. Usually there are not more than two, three, or four crops of eruption. Almost invariably it first appears on the back, chest, and abdomen, but occasionally first on the face or limbs. It consists of small rose-coloured macules which fade when the skin is stretched: in outline they are irregularly circular or elongated, their shape not infrequently foreshadowing that of the subsequent vesicles. Occasionally they attain almost the size of blotches. In the course of a very short time—an hour or two usually—the lesions are raised and slightly hard—not, as a rule, the well-defined hardness of small-pox papules, but a diffuse hardness; and many are faintly acuminated in the centre when the vesicle is just beginning to form. Some of the smaller papules, however, become hard and more or less "shotty." The lesion is usually superficial, being more on the skin than in it, as is the case in small-pox. Lesions of the same age shew, in many cases, great disparity in their evolution. Some of the macules never emerge from the macular stage, but fade in the course of twenty-four hours; others become papules, subsiding after a day or two; while a few shew minute vesiculation, and others become full-sized vesicles. After the appearance of successive crops the eruption is present in all its stages: macules, papules, clear shining vesicles, desiccating unruptured vesicles, and crusts. The vesicles, which are often smaller than the rose-coloured macules, arise as a rule in the central portion of

the papulo-macules. At the limit of their growth, which may be attained in from six to twenty-four or thirty-six hours, they are circular or of an elongated dome-shape and filled by clear serum. They are transparent, shining, tense, and collapse if pricked and their contents pressed out. They are often encircled by a pink or red areola, which may be broad and irregular in outline, and is usually narrower on the face and extremities than on the trunk. The characteristic vesicle is not depressed in the centre ; occasionally, however, some vesicles shew a minute central depression. If circular, the vesicles vary in size from that of a small pin's head to a fair-sized pea ; if oval or elliptical, their long diameter measures about three-sixteenths to three-eighths of an inch. When the vesicle ruptures, the whole of the fluid may escape and the walls collapse : if only a portion escape, the central part of the vesicle collapses more completely than the periphery ; a minute crust forms in the centre at the point of rupture, the vesicle then shewing a central depression. Many of the vesicles get ruptured by scratching or other forcible means ; but some large and many small ones desiccate unruptured, forming rounded, light to dark brown prominences of various sizes, not unlike the unruptured desiccating vesicles of small-pox ; the desiccated contents and epidermis fall off at periods varying from five or six days to two or three weeks, exposing a reddened, flat, or slightly indented epidermis on which some desquamation takes place.

Many vesicles soon after rupture increase in size, shewing puckered margins, purulent contents, and red areolæ ; inflammation and ulceration take place underneath, often extending considerably beyond the original limits of the vesicle. Dirty yellow or blackish impetiginous crusts form and come away at periods varying from about a week to ten days or longer, often leaving an ulcerated surface with a central excavation. The ulceration heals quickly as a rule, but the skin remains reddened for a considerable time, and more or less permanent pitting results in many cases. Ulceration is more frequent in children than in adults, and on the face and trunk than on the limbs.

Most vesicles rupture while the contents are clear, but some remain unruptured, the serum becoming cloudy, or puriform, but rarely so frankly purulent as in small-pox. In some few cases of chicken-pox very little fluid exudes into the vesicles, in which case they are raised, flat, and white in appearance, not unlike a small empty blister.

The vesicles on the hands and feet are almost invariably small, circular, hard, contain a little fluid, only in the rarest instances shew a central depression, and are often indistinguishable from the vesicles of modified small-pox ; those on the forearms and legs often have these characters, and, if the eruption be copious, some of those on the trunk likewise. The vesicles may not exceed a dozen, or there may be some hundreds, and in confluent cases several thousands. Often there are 50 to 100 or 200. I have seen an eruption, on a girl of fourteen years of age, so abundant as to be almost confluent on the trunk and extremities.

The eruption appears on the mucous membranes usually at the same

time as on the skin, but it may be later and occasionally precedes the skin eruption. Commencing as small red papules the lesions increase in size, soon shewing commencing vesiculation. The vesicles are mature in about twenty-four hours, usually having a reddened base. They rupture after a short time and collapse, and have the appearance of small empty blisters with red areolæ ; later, shallow ulceration ensues, in most cases healing in a few days, but sometimes aphthous ulcers result. The lesions on the mucous membranes are usually few in number.

The distribution of the eruption is, in the majority of cases, characteristic of the disease. It is most abundant on the trunk and sometimes also on the scalp ; less abundant on the face, arms, and legs, and least of all on the hands and feet ; the palms and soles being very often free from eruption. In rare exceptions to this rule it is found more abundantly on the face and extremities than on the trunk, the distribution resembling that of small-pox. It also appears on the buccal mucous membrane, hard and soft palate, tongue, pharynx, tonsils, vulva, male genital organs, and, in very rare instances, on the larynx, conjunctiva, and urethra. The character of the vesicular eruption varies as a rule with its distribution. Circular, oval, and elliptical vesicles are usually to be seen on the trunk, thighs, and arms ; on the face and scalp, legs, and forearms they are mostly circular, and on the hands and feet almost invariably so.

Symptoms.—In the majority of instances, chicken-pox is quite a mild disease, and free from danger to life, symptoms of illness being usually slight, and sometimes absent. Many patients, however, especially when the skin lesions are fairly abundant, suffer discomfort from the itching and irritation of the vesicular eruption ; and there may be restlessness and occasional sleeplessness. The appetite is often unimpaired, recovery being usually rapid and complete. Painful micturition, with sometimes retention of urine in males, may be caused by vesicles on the prepuce or urethra, or on the labia in females. The pyrexia is as a rule unimportant, and may be absent in very mild cases. If present, the temperature often rises concurrently with, or shortly after, the commencement of each crop of eruption, usually falling to normal between the crops. It ranges from just above normal to 100° or 102° F., sometimes rising to 103° or 104° F., rarely higher. If the lesions heal quickly the pyrexia is over soon after the last crop of spots has appeared. The pulse is only slightly accelerated in the milder cases, but in severe attacks it may be much quickened. The severity of the symptoms and duration of the acute stage depend chiefly upon the number of crops and abundance of the eruption, the number of vesicles that become mature, the degree of suppuration of the vesicles, and the number of lesions in which inflammation, ulceration, or necrosis ensue after rupture, great variations being observed in these respects. In a large number of cases the ruptured vesicles shew little tendency to inflammation and ulceration ; thin crusts form, under which the skin heals in a comparatively short time, while the vesicles that remain unruptured become slightly purulent,

shrivel, and desiccate, the dried contents and epidermis falling off in the course of a week or a fortnight, rarely adhering longer. In such cases the symptoms are quite negligible. In a considerable number of cases, however, many of the ruptured lesions exhibit ulceration under the impetiginous crusts, while the mature unruptured pocks become more or less purulent, some rupturing and scabbing, others desiccating unruptured. There is some swelling and tenderness of the skin, the patients being often irritable and restless and experiencing pain and discomfort on movement. The degree of pyrexia varies considerably; it may reach 102° or 103° F., rarely rising to 104° or 105° F., falling usually about the end of the first week, often by crisis. It does not rise again in many instances, but when the eruption is very abundant there may be a secondary rise of temperature during the second week, due to extensive suppuration under the crusts, with a certain degree of dermatitis, and in some cases slight necrosis of the lesions.

When the eruption is very abundant, in some instances assuming a slight degree of confluence, there is considerable swelling of the skin, with much discomfort, constitutional disturbance, restlessness, sleeplessness, and pyrexia. Cases of this nature shew considerable resemblance to small-pox when the eruption is at its height and many of the lesions are purulent, especially if the eruption be copious on the face and extremities. From suppuration and inflammation of many of the lesions there is often secondary fever with symptoms of some severity, and superficial abscesses or boils may follow. In some instances bullæ are formed by peripheral enlargement of individual, or the coalescence of adjoining, vesicles. The bullæ rupture, crusts form, ulceration and inflammation of varying extent following. In extreme cases, the epidermal covering of the bullæ comes away in large masses, exposing a raw, oozing surface; the symptoms increase in severity, and there is considerable pyrexia. If a large extent of skin be involved and the patient be very young death may occur. In one such case under my care, an infant of thirteen months, the eruption was extremely abundant, adjoining vesicles coalesced, forming large bullæ filled with blood-stained serum. When these ruptured the epidermis peeled off extensively, the skin became swollen and inflamed, there was a continuously high temperature, 102°-103·8° F.; from the second day of illness the pulse became very rapid and increasingly weak, the child dying on the sixth day of the disease. Nisbet has recorded a case of confluent chicken-pox in an infant of eight-and-a-half months, fatal on the tenth day. Confluent eruptions in chicken-pox are rare.

Necrosis following secondary pyogenetic infection of the ruptured lesions occasionally occurs even in cases treated under quite favourable conditions, while among the children of the poor it is not infrequent. It may be slight and limited to the original area of the lesion, not extending deeply into the corium. The lesions on the trunk are those most frequently involved. The skin under and surrounding the crusts is reddened and indurated. On the separation of the crusts ulcers of varying sizes, with central excavations, are exposed, which, on healing, leave oval or

round pits according to the shape of the primary lesion. There is usually febrile disturbance, but, unless a considerable number of lesions be involved, the symptoms are not severe. When necrosis affects the skin more deeply the disease assumes the gravity of gangrenous chicken-pox.

Gangrenous Chicken-pox.—The number and situation of the lesions in which gangrene occurs, and the depth and extent of the surface involved vary much in different cases. The scalp and trunk are the favourite situations; in many, necrosis is limited to the skin, but in others it extends more deeply. The lesions shew firmly adherent grey or black flattened scabs, with irregular pustular borders and red areolæ, necrosis taking place under the scabs. All degrees of severity are met with, from comparatively superficial to very deep lesions, the former being much more frequently seen than the latter. Sometimes neighbouring lesions unite to form large sloughs. After a time the sloughs separate, exposing sharply defined, conical, ulcerated excavations of varying depths, in rare cases so deep that portions of the muscles are exposed, or the bone may be bared if the scalp be affected. The lesions usually heal quickly after separation of the sloughs. When healed the skin is deeply reddened, the pitting and cicatrisation, which always result, being proportionate to the necrosis of the skin and underlying tissues. The constitutional symptoms may be severe, the pyrexia high; pleurisy, pyæmia, and secondary abscesses may follow. Gangrenous chicken-pox mainly occurs in young children under four years of age, being commoner in females than in males. When the lesions are numerous and deep the danger to life is considerable, especially in very young, unhealthy, and ill-nourished children, death sometimes supervening. Severe cases are comparatively rare, though the slighter degrees of necrosis, affecting a limited number of the lesions, occur not infrequently. It should not be forgotten that gangrene is a pathological condition superadded to the normal lesion of chicken-pox after rupture of the vesicles. Unruptured chicken-pox vesicles do not become gangrenous.

Hæmorrhagic Chicken-pox.—This form is very rare, and the vesicles are usually few in number. Large and small ecchymoses appear on the skin with hæmorrhage into the cutis under the vesicle, accompanied by hæmatemesis and melæna. The symptoms are severe, but recovery usually takes place.

Complications and Sequels.—Apart from the secondary affections of the skin lesions, complications and sequels are of rare occurrence. Erysipelas, boils, and superficial abscesses sometimes follow, and parotitis has been noted. Laryngitis has been recorded by Marfan and Halle in two cases. In one the dyspnœa was so urgent that tracheotomy had to be performed, the child making a good recovery. In the other, which proved fatal, a shallow ulcer about the size of a pea was found on the posterior part of the right vocal cord, probably the result of a vesicle. Nephritis occurs in rare instances during the first and second week; recovery from it is usually rapid and

complete except in unhealthy children. Brown has recorded two cases proving fatal several years later. Bronchitis and bronchopneumonia occur. I have seen a case complicated with pneumonia, and another, a rather weakly infant, developed bronchitis, both cases proving fatal. Acute miliary tuberculosis has been known to follow. Periostitis of the femur (Steiner) and of the humerus (Brunner) have been noted, followed in the latter case by double parotitis, left otitis media, and purulent pericarditis. Acute suppuration of knee and elbow-joints with septic endocarditis has been reported by Braquehaye. Paraplegia, passing away in convalescence, has been noted in a rachitic child a fortnight after the onset of the disease. Permanent pitting and scars are a frequent result of chicken-pox. Trousseau noted a bullous eruption like pemphigus, lasting six or eight weeks, occurring fifteen, twenty, thirty, or forty days after the commencement of the illness. Mr. Jonathan Hutchinson has recorded a number of cases that were followed by a persistent mixed papular and vesicular symmetrical eruption, avoiding flexures, prone to affect the soles and palms, and very intractable.

Duration.—In cases uncomplicated by ulceration or gangrene, the acute stage lasts two or three days if there be only one crop of vesicles; three to seven, if several crops appear, and sometimes seven, ten, or twelve days. Convalescence is usually rapid. Infectivity lasts from the appearance of the eruption until the skin is free of crusts and desiccated unruptured vesicles and pustules. In many cases a fortnight suffices for this, but as some of the crusts and desiccated vesicles and pustules adhere to the skin more tenaciously than others, the process may not end until three or four weeks from the commencement of illness. The desquamation that follows after the healing of gangrenous surfaces is not to be regarded as contagious.

Chicken-pox frequently co-exists with whooping-cough, scarlet fever, measles, or diphtheria (*vide* p. 843).

Diagnosis.—The differential diagnosis of chicken-pox and small-pox (for which disease it is most commonly mistaken) is discussed in the article "Small-pox" (p. 522). Acne and vesicular and pustular syphilitic eruptions should not cause much difficulty. In impetigo contagiosa the face is mostly affected, the trunk rarely, the mucous membrane of the mouth not at all. In molluscum contagiosum the small tumours are umbilicated and filled by a soft, white, granular substance that can be easily squeezed out. Small patches of herpes on the abdomen and chest may look not unlike chicken-pox. By the aid of a lens the minute vesicles can be seen, and any doubt removed.

Treatment.—Mild cases do not require special treatment, but it is advisable when the eruption is at all copious to keep the patient in bed for a short time and to give light diet if the appetite be impaired. A dusting powder composed of pulv. acid. boric., zinc. oxid., and starch in equal proportions will often relieve the itching and discomfort. Dr. J. D. Rolleston recommends a boric bath, night and morning (boric acid crystals, 1 oz. to 1 gallon of water). He finds that the cutaneous

irritation and itching are relieved by this means, the tendency to scratch checked, the subsequent dermatitis being reduced to a minimum. In order to effect the early separation of the impetiginous crusts, boric acid dressings or fomentations should be employed. Lint soaked in olive or castor oil is a useful application when there is troublesome ulceration and crusting. If gangrene set in, boric or other suitable fomentations may be applied. Hæmorrhagic, gangrenous, and severe cases require careful nursing, ample nourishment, and sometimes alcoholic stimulants.

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SMALL-POX

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SYNONYMS.—Arabian (Razes), *Jadari*; Latin, *Variola* or *Variolæ*; French, *La petite Vérole*; Ital. *Vajuolo*; Span. *Viruelas*; Germ. *Blattern*, *Menschenpocken*; Danish, *Kopper*; Modern Greek, *Εὐλογία*. In Scotland still written *The Pocks* (pokes or pockets of matter).

Definition.—An acute infectious disease, characterised by pyrexia and a general eruption of minute red macules, which in about eight days pass through the successive stages of papule, vesicle, and pustule.

History and Prevalence.—See p. 767.

Susceptibility.—Of unvaccinated persons very few are insusceptible to small-pox; this insusceptibility has been variously estimated at from 1 to 5 per cent. Probably it is not more than 1 or 2 per cent; and most susceptible persons contract it on first exposure to infection. Small-pox attacks all races, but the negro is believed to be the most susceptible. Hospital records shew that more males are attacked than females.

It is said that infants are not so susceptible to small-pox as children and adults, but this is doubtful. Of infants subjected to infection

that have come under my observation, I have seen only one that failed to contract the disease, and that was a child born at the full time during the convalescence of the mother from an attack of discrete small-pox. There was no evidence that the child had had small-pox in utero. It was insusceptible not only to small-pox—so far as a month's residence in a ward full of small-pox patients without contracting the disease was evidence of its insusceptibility—but also to vaccinia. Infants, as a rule, are less exposed than children and adults, not only to the infection of small-pox, but to that of other infectious diseases.

Pregnancy and childbirth do not appear to increase the susceptibility to small-pox, nor do persons suffering or convalescent from other acute infectious diseases appear to be more susceptible to it than those in ordinary health. On the contrary, there is some reason to believe that, in the acute stage at least, they are less susceptible to it than are healthy persons.

In countries where small-pox had been widely prevalent for generations, it was, before the introduction of vaccination, a disease mainly of children, as are scarlet fever, measles, whooping-cough, and diphtheria at the present day; nearly all susceptible individuals contracted it in infancy or early childhood, and the majority of the survivors were thereby protected against it for life. But when it attacks an unvaccinated population for the first time, or after a long period of immunity, all ages are affected alike.

Small-pox has at one time or another prevailed in every quarter of the globe, with the exception of Australia, where, although introduced on several occasions by immigrants, its spread has been promptly checked by the isolation of the sick.

Climate and Season.—As regards the influence of climate, it would appear that small-pox is more prevalent in tropical than in temperate countries. In the former there is said to be lessened prevalence during the hot and also during the rainy seasons.

The season of the year affects its prevalence in some degree. In temperate climates summer is the season of least, and spring, autumn, and winter the seasons of greatest prevalency. I have frequently noticed that in outbreaks commencing in autumn there has been a sudden drop in June of the following year, and that the lessened incidence continued during the summer months. It is not probable that this drop is due only to the more airy habits of life in summer.

Morbid Anatomy.—*Skin and Mucous Membranes.*—The most recent investigation into the pathology of small-pox has been made by Councilman of Harvard. His summary, condensed in some parts, of the lesions of the skin and mucous membranes is as follows:—The specific lesion of small-pox is a focal degeneration of the stratified epithelium, vacuolar in character, and accompanied by serous exudation and the formation of a reticulum. The fully developed product of these processes is a characteristic multilocular pock or pustule. The occurrence of these lesions is sharply limited to the stratified epithelium of the skin and of

the mucous membranes. The lesions may be few or numerous, and bear no fixed relation to any anatomical structure of the skin. The lesions pass through progressive stages, and reach a climax of development about the eighth or ninth day from their start.

The typical lesion is best seen on the skin. It begins with degeneration of the cells of the deeper layers of the epidermis accompanied by exudation at first serous, later more or less cellular, the products of which are contained within the spaces of a reticulum formed by degenerated cells. The exudate increases in amount, and the spaces of the reticulum enlarge, until the fibres finally rupture and the lesion becomes a distended pustule. This development may take place wholly within the epidermis, and the fluid contents of the pock be separated from the corium by comparatively intact cells; or the corium may form the bottom of the pustule, in which case there is usually necrosis of the papillary layer. The subsidence and repair of the lesion (if the pustule remain intact) are accompanied by the removal of the fluid portion of the exudate by absorption and drying, and by the regeneration of the epidermis, in the course of which the residual mass of degenerated epithelial cells, leucocytes, and débris enclosed between the two layers of the horny epidermis, the old and the newly formed, is exfoliated. The complete evolution of the lesion occupies about two weeks. Associated with the lesions of the epidermis there may be œdema, cellular infiltration, and hæmorrhage in the corium.

The lesions of the mucous membranes are in degree proportional to the extent and to the severity of those of the skin. At an early stage of development they resemble the lesions of the skin, but, owing to the different structure of the mucous membrane, the resemblance is lost in the course of their evolution. In the absence of a restraining horny layer the degenerated epithelial cells are cast off, and the vesicle within the epidermis is rarely seen, the pustule never.

Contained within these lesions of the skin and mucous membranes, and determining their specificity and occurring chiefly in the cells of the rete mucosum, is the parasite peculiar to small-pox; in its younger or cytoplasmic form it is present in the protoplasm of the epithelial cells of early lesions, and of such of the older lesions as are extending; in its intranuclear form it is, for the most part, in more advanced lesions. No parasites have been found in any lesion of the skin in which repair was well advanced. (For a description of the parasite cytoryctes, see Prof. Minchin's article on the "Protozoa" in the volume on Tropical Diseases.)

Accompanying the later stages of the specific lesions, and simulating them in other forms, are others, bleb-like, in which the entire epidermis is elevated by fluid exudate; from these the parasite is absent.

The changes that take place in the vesicle during the stage of pustulation are described by Unna as follows:—From the fifth day onward the appearances (in the vesicles) completely alter; the blood-vessels are now distinctly dilated, not only on the surface but through the whole cutis. A full stream of leucocytes, attracted, no doubt, by the germs

lying dead in the tissue, runs through the whole cutis, reaches the papillary layer, invades the pock, and fills the cavity proper with white corpuscles. This process attains its acme in a few days, and, if the horny layer remain intact, the whole pustule is completely filled with white corpuscles and is converted into an almost solid tissue; but if the horny layer yield, there is more or less profuse suppuration, which lasts for a time or rapidly ends in the formation of a crust. The spontaneous pustulation at the end of the first week is without doubt to be attributed to the poison of the disease itself; the prolonged suppuration must certainly be attributed to the addition of pyogenetic organisms. Unna ascribes the umbilication of the vesicle partly to reticular degeneration, partly to epithelial œdema, the latter being always limited to the periphery.

Hair-follicles play only an accidental part in the causation of the umbilication of the vesicle. In a considerable number of cases of natural small-pox, owing to hypertrophy of the papillæ at the site of the pustule, an elevation of skin is seen when the crust has fallen off; the new discoloured epidermis, being raised well above the level of the unaffected skin, imparts to it a nodulated, in many cases a tubercular appearance, usually most marked on the face. After a time the hyperæmia subsides, the nodules shrink, and the skin in many cases regains its natural smoothness.

The characteristic lesion of small-pox develops in the skin, lips, tongue, buccal mucous membrane, gums, hard and soft palate, tonsils, anterior and posterior nares, pharynx, epiglottis, larynx, trachea as far as the bifurcation and occasionally beyond, and rarely in the œsophagus; also on the lower part of the rectum, the anus, the vulva, the lower portion of the vagina, the scrotum, the penis, glans penis, and also on the conjunctiva; but not on the healthy cornea or on serous membranes.

Some authorities state that a diphtheritic condition of the fauces and pharynx occurs not infrequently. This appears to me to be a mistake. In cases with a large amount of eruption on the fauces, pharynx, and palate, the swollen tissues, with ragged shreds of mucous membrane and epithelial débris, often present an appearance not unlike the dirty disintegrating membrane seen in diphtheria. That faucial diphtheria may occur I do not doubt, but I have not seen it complicate small-pox, nor have I seen a case of small-pox followed by the paralytic sequels of diphtheria. But I have noted membrane in the larynx in one or two cases, and once in the trachea, similar to that seen in laryngeal and tracheal diphtheria. If there be eruption in the larynx, the mucous membrane is swollen and injected, often shewing minute ecchymoses.

Lungs and Pleuræ.—Bronchitis, bronchopneumonia, hypostatic congestion and pneumonia, lobar pneumonia, pleurisy, and empyema are all met with.

The *Muscles* shew granular and fatty degeneration.

The *Heart* is pale and flabby, shewing cloudy swelling and fatty change. The blood is dark in colour and coagulates slowly. There is

some degree of leucocytosis in the stage of pustulation and later, but perhaps not as much as in some other acute infections.

Abdominal Organs.—The *liver* may be, but is not usually, congested. In cases dying after the fifth day it is generally enlarged, being pale, soft, and shewing considerable fatty change, with infiltration of leucocytes between the cells of the lobules and into the interlobular spaces. Occasionally there is thrombosis of minute vessels. The *spleen* is increased in size, the Malpighian bodies being enlarged, the pulp soft and infiltrated with leucocytes, the mononuclears predominating. Nucleated red corpuscles are found. In rare cases there are thromboses of minute vessels, and cellular necroses; sometimes there are hæmorrhages. The *kidneys* shew interstitial or tubal inflammatory changes, with swelling and fatty degeneration of the cortex. The *suprarenals* shew cellular infiltration and often fatty changes in the cells. The *intestinal mucous membrane*, especially that of the small intestine, is congested. Peyer's patches may be congested and swollen. Sometimes ulceration of the intestine occurs, probably due to minute emboli. The *testicles* shew in some cases parenchymatous inflammation and anæmic focal necroses, which appear to be specific to the disease. In other cases there is inflammation of the tunica vaginalis with fibrinous effusion.

Lymphatic Glands.—Some observers have found focal necroses. Roger says that the changes are analogous to those found in leukæmia.

Bone-Marrow.—There are focal necroses, hyperplasia of myelocytes, but a reduction or absence of polymorphonuclear leucocytes.

Brain and Spinal Cord.—Occasionally cerebral hæmorrhage occurs from rupture of a vessel, and a large quantity of blood is extravasated. In fatal cases of coma nothing is noted except congestion and œdema of the meninges, and in some cases hæmorrhage under the pia mater. Zuelzer has observed hæmorrhages into the nerve-sheaths, and it is not improbable that some of the nervous sequels may be due to minute hæmorrhages in the cerebrum and spinal cord. In some cases of paraplegia small foci of softening have been found in the grey and white substance of the cord. Welch and Schamberg record a case of complete paraplegia with incontinence of urine and fæces, in which there was great softening of the cord in the region of the lower dorsal and upper lumbar vertebræ. When the dura was punctured the softened cord ran out like pus. In some cases diffuse myelitis, affecting mostly the anterior horns, is found.

Morbid Anatomy of Hæmorrhagic Cases.—When sub- and perivesicular hæmorrhage takes place, it is into the whole thickness of the cutis; but the serum exuded from the hæmorrhagic surface is nearly always free from hæmoglobin or blood-corpuscles.

The early changes in the skin are similar to those observed in the development of the pock; swelling and degeneration of the deeper cells of the epidermis, with dilatation of the blood-vessels of the corium and hæmorrhages, mostly in the papillary layer.

The purple petechiæ, and the inky or deep violet coloured circular spots, are caused by hæmorrhage into the cutis, which sometimes extends

to the subcuticular tissue. It is probable that these skin hæmorrhages are due to transudation of the red corpuscles through the walls of the capillaries. The bruise-like swellings are caused by hæmorrhage into subcutaneous and intermuscular connective tissues.

Subconjunctival and retinal hæmorrhages occur. Deep-seated hæmorrhages take place into the muscles, connective tissue, and mediastinum. Subpleural hæmorrhages — visceral, parietal, and diaphragmatic — and hæmorrhages into the lung substance, are common. Subperitoneal hæmorrhages occur on the surface of the liver, spleen, pancreas, mesentery, and large and small intestine. Extensive extravasations of blood take place in the loose tissue and fat round the kidneys, and extend along the course of the psoas muscle into the pelvis. Hæmorrhages into the liver and spleen are very rare.

Kidneys.—Subscapsular hæmorrhages are of frequent occurrence, but hæmorrhage into the cortex and pyramids is very rare. There is often a copious extravasation of blood into the tissues between the calices and the substance of the kidney, whereby the calices are compressed, and some of them detached from the papillæ, the space being filled with blood. On longitudinal section of the kidney the blood-clot appears to fill the calices and pelvis; on closer examination, however, it is seen that it lies not in the calices and pelvis, but between these and the kidney substance.

The *liver* is usually normal in size and colour, but it is sometimes dark; fatty change has been noted in some instances.

The *spleen* is usually small, firm, and dark, but sometimes it is enlarged, and may shew hæmorrhages, infarcts, and nucleated red corpuscles.

Hæmorrhages occur into the mucous coat of the bladder, uterus, vagina, Fallopian tubes, ovaries, testicles, bone-marrow, synovial membranes and cavities of joints.

Bone-Marrow.—There is increase of the nucleated red cells, diminution and fatty degeneration of the white cells.

Digestive System.—Hæmorrhage occurs into the mucous membrane of mouth, pharynx, and nose. In the stomach there are often masses of small red and purple hæmorrhages in the mucous and subcutaneous coats. They occur in the large and small intestine, and also in the rectum.

Heart and Blood-vessels.—In pure hæmorrhagic cases the heart is contracted, firm, and dark-brown in colour. The cavities contain little if any blood or clot, and the arterial trunks are usually almost empty. Hæmorrhages occur under the pericardium and endocardium, but not, so far as I have seen, in the valves or blood-vessels.

Contagiousness.—Boerhaave, at the beginning of the eighteenth century, first proved that small-pox was spread by contagion exclusively, although its contagious nature had for a long time been known. Since the Brahmins and Chinese practised inoculation it is probable that they recognised this feature of the disease. The Arabs were cognisant of it, and it was known in England as early as the fourteenth century. The

contagion may be either direct or indirect, and there is good evidence to shew that the virus may be carried from a small-pox hospital, by the air, a considerable distance, without losing its infectivity. The virus enters the human body by the mucous membrane of the nose, mouth, or respiratory tract; some believe also by the mucous membrane of the stomach. It may be communicated from the sick to the healthy by—(*a*) Persons suffering from small-pox; (*b*) Bodies of persons who have died of small-pox; (*c*) Infected articles, and perhaps by flies and domestic animals; (*d*) Healthy third persons; (*e*) By the air to persons living at some distance (aerial infection); (*f*) Inoculation.

(*a*) Small-pox patients are capable of communicating infection to others, perhaps during the stage of incubation, certainly during the initial stage, and right through the disease till not a trace is left on the skin of desiccated pustules, scabs, and powdery débris. But the infection is much more virulent at certain stages of the disease than in others; it is most virulent during vesiculation, pustulation, and scabbing, less so during the initial stage and the first and second days of rash, and least of all during the incubation-stage. The distance at which a single patient may communicate infection to a healthy person varies from the closest contact to a few yards, much depending upon the ventilation of the apartment. As a rule a susceptible person will be infected merely by entering the room or ward occupied by the patient. The severity of an attack of small-pox appears to be determined more by the personal susceptibility of the recipient of the contagion than by the severity of the disease in the person imparting it. I have known the mildest form of modified small-pox in one person to cause pure hæmorrhagic small-pox in another, and vice versa.

(*b*) The bodies of the small-pox dead can communicate infection.

(*c*) Infected articles such as bedding, wearing apparel, books, toys, coins, furniture, rags, or anything handled by patients, are capable of communicating infection. Infected rags have frequently given rise to outbreaks of small-pox. Flies and domestic animals may possibly be carriers of infection.

(*d*) Healthy third persons in attendance on patients may communicate infection to others, either by means of their clothing, or by the hair, which readily retains the particles of dried small-pox matter which permeate the air of the infected room.

(*e*) It may be conveyed directly by the atmosphere from a small-pox hospital to persons living at some distance. How far is a point on which there is great difference of opinion. Mr. Power, in his investigations at the Fulham Small-pox Hospital, proved that the incidence of small-pox bore a very exact relation to propinquity to the hospital. The incidence on every 100 houses within the special area (a radius of a mile from the hospital) was as follows:—On total area, 6·37. On small circle (one quarter mile), 17·35. On first ring (quarter to half a mile), 9·25. On second ring (half to three-quarters of a mile), 6·16. On third ring (three-quarter to one mile), 2·57. The influence was greatest when admissions to hospital were beginning to increase. The comparison held good with

regard to successive epidemics, and he did not regard the hospital administration as responsible. Dr. Barry shewed that a similar incidence of small-pox around the hospital prevailed at Sheffield during the epidemic of 1887-1888; and some confirmatory evidence of a like character has been obtained from other localities at home and abroad. On the other hand, many medical officers of health, basing their opinion upon the more recent experience of the incidence of small-pox in the neighbourhood of small-pox hospitals generally, are disposed to regard the validity of Mr. Power's conclusions as open to question. They hold that further knowledge and investigations are necessary before a final judgment can be formulated on this matter.

(*f*) Inoculation is not practised in civilised countries; it is illegal, and has chiefly a historical interest. Cases of accidental inoculation do, however, occur occasionally, such as inoculation of mother from her infant at breast, or vice versa, and in other ways.

The Contagium of Small-pox.—The exact nature of the specific contagium has not been conclusively determined, but present knowledge favours the view that it is a parasitic protozöon, probably a sporozöon, and that it is present in the vesicular lymph, the pustules, and the blood.

Incubation-Period.—When a person receives the specific infection of small-pox there is in most cases a definite interval between that time and the onset of the earliest symptoms, during which no apparent deviation from normal health is noted. This interval varies in different individuals between extremes of five days and twenty or more; usually it is ten to twelve days, but not infrequently nine, thirteen, or fourteen days. Curschmann records a case of five days' incubation; Welch and Schamberg one of five and a half days; I have seen it as short as seven; and Armstrong (*Lancet*, 1886, vol. i. p. 715) has given particulars of a case in which it appeared to be twenty-one days. Some continental observers have noted it to be twenty, twenty-two, and twenty-three days, but such lengthened incubation-periods, as well as the extremely short, are very exceptional. In a few rare cases symptoms of malaise are noted from the date of reception of the infection.

Initial Symptoms.—The onset as a rule is sudden, and the early or initial symptoms are usually severe and distinctive of the disease. The most constant symptom is headache, in most cases frontal. It is often intense and throbbing, and is aggravated by movements. Backache, the next most constant symptom, is, of all the initial symptoms of small-pox, the most characteristic, headache being frequently met with in the early stages of other acute infectious diseases. The backache is lumbar and sacral, is usually severe, in many cases excruciatingly so; the pain often extends from the sacrum down the thighs and legs. Both headache and backache last till the eruption comes out, or for some little time after. Rigors, severe or slight, are often present from the commencement. Epigastric pain, accompanied by nausea, retching, and vomiting, is also an early and, especially in children, a very usual symptom. The vomiting and retching are sometimes excessive, the patient being unable to retain

even the smallest quantity of nourishment. Anorexia and thirst are present in every case. The fauces do not as a rule present any abnormal appearance; the tonsils may be enlarged, and in hæmorrhagic cases purple hæmorrhages may be noticed on the soft palate. The breath is often fetid and the tongue coated with a white or dirty white fur; the skin is usually hot, dry at first, but afterwards moist or even sweaty. Pallor is often marked, and may be accompanied by coldness of the extremities; but in many cases there is flushing of the head and face. Constipation occurs in nearly all cases. In children drowsiness is often present, and occasionally convulsions. Coma, rare in adults, is met with in children, and may follow convulsions. I have seen profound coma lasting till the third day of the eruption. Delirium is sometimes present on the second or third day, and is occasionally marked; but is usually only slight. It is, however, sometimes accompanied by paralysis of the upper and lower extremities. In other cases there is great mental disturbance, with loss of co-ordination of movements, and aphasia; in some instances the patient has been thought by the relatives to be drunk. Most patients are sleepless and restless. Vertigo is by no means rare. Paraplegia has been noticed, and also retention of urine. Prostration often accompanies the other symptoms, and the patient usually takes to bed or sits over the fire. In females menstruation often occurs before the usual menstrual period; in many cases more than the usual quantity of blood is lost, and in hæmorrhagic cases the amount may be large or even excessive. The urine is diminished in quantity, its specific gravity is increased, and it usually contains urates in abundance, but the chlorides are diminished; albumin may be present, but rarely in large quantity. There may be blood in the urine, but this occurs infrequently, and mostly in cases that afterwards prove to be hæmorrhagic. The temperature, except in some hæmorrhagic cases, is high from the onset of the initial symptoms. At first it is 100° to 101° F., and may reach 104° F. on the first day; on the second day it may be as high as 105° or 107° F. It remains raised, with very slight morning remissions, until the eruption comes out. The pulse is rapid, often 110 to 120 or more in adults, and in children 150 or more. In most cases it is full, fairly strong, and regular; but in cases accompanied by much depression it is weak and rapid. In pure hæmorrhagic cases it is often soft and compressible; such patients not infrequently experience a sensation of cardiac and respiratory oppression. The respiration is quickened, and when coma is present it may be stertorous. There is no enlargement of liver or spleen.

The initial symptoms are present at the onset of the disease in vaccinated and unvaccinated subjects, usually abating when the eruption comes out, and subsiding when it is fully out. In vaccinated persons the initial symptoms often disappear quite suddenly very soon after the appearance of the eruption. The epigastric pain and vomiting are usually most marked early in the initial stage; but sometimes, especially in hæmorrhagic cases, vomiting may last until the termination of the disease. The *average duration* of the initial stage is two days, but it may not be

more than one, or it may be three or more. In some cases the initial symptoms are gradual in onset, mild in character, and may be of short duration; in such cases the attack usually proves mild, but the converse does not hold good: patients whose symptoms in the initial stage are exceedingly severe, or who are convulsed or comatose, may pass through mild attacks, but most cases of severe small-pox are ushered in by severe initial symptoms.

Initial Rashes.—Along with the initial symptoms just enumerated, a series of eruptions may appear on the skin, which, from their occurrence in the initial stage of the disease, are known as initial rashes. These may be divided into two great groups—(I) the Erythematous, and (II) the Hæmorrhagic.

I. *Erythematous Rashes.*—These may be either (*a*) general or (*b*) partial.

(*a*) *General Erythemas.*—These are usually scarlatiniform or morbilliform in appearance. In many cases they do not cover the entire surface of the skin, limited areas being free from eruption. They are usually to be noted on the trunk, limbs, and, to a less extent, the face and neck. They may appear on the first day of illness, more generally on the second, sometimes on the third, fourth, or even fifth day. They persist for a period varying from two to five days, disappearing in some instances before the characteristic eruption of small-pox comes out, in other cases simultaneously with its appearance, and in others not until one, two, or three days after the small-pox eruption is out. They reach their height in from twenty-four to forty-eight hours, and often disappear completely twelve hours thereafter, and leave no stain. In other cases they pass off more slowly. The general erythemas are of more frequent occurrence in adults than in children; the morbilliform is sometimes seen in the latter, but the scarlatiniform has not been observed, as far as I know, in any one under ten years of age.

The *scarlatiniform erythema* resembles the eruption of scarlet fever, but it differs from it in being usually less bright in tint and less punctate in character. In the groins, axillæ, and flexor surfaces of joints it is often of a deeper tint than elsewhere. It is not raised; it disappears on pressure, and is not accompanied by vivid faucial inflammation or enlargement of the cervical or submaxillary glands. But occasionally an intensely vivid rash is seen, which appears sometimes on the first, more frequently on the second day of illness, covers the entire surface of the skin, and is at first of a uniformly brilliant deep-red colour, which in some hæmorrhagic cases deepens almost to the tint of an Indian red. It disappears on pressure, is often the precursor of grave hæmorrhagic symptoms, and lasts a varying period; in hæmorrhagic cases it may last till death; in other cases until the second or third day after the appearance of the characteristic eruption of small-pox, when it fades gradually and leaves no discoloration of the skin.

The *morbilliform erythema* is of the pink colour of measles, is very slightly, if at all, raised, disappears on pressure, and shews in parts the crescentic appearance often noticed in measles. It usually reaches its

height within twenty-four hours of its first appearance, and fades quickly either just before the characteristic eruption of small-pox appears, or soon after, leaving no stain. The maculæ are from the first larger than the minute maculæ of the early stage of measles eruption. The rash spreads over the whole body more quickly than that of measles, and in the great majority of instances is not preceded or accompanied by catarrh, sneezing, or cough; not infrequently, however, there is considerable suffusion of the eyes. *Urticarial* rashes have sometimes been noted in the initial stage of small-pox.

(*b*) *Partial Erythemas.*—These are usually scarlatiniform or morbilliform in appearance, and affect the flexor or extensor surfaces of joints and circumscribed areas of other parts of the skin. If limited to flexor surfaces they are distributed on the lower part of the abdomen, the inner surfaces of the thighs, and the flexor surfaces of the joints of the extremities, palms of hands, and insteps of feet. In other cases they are limited to flexor surfaces of limbs, or to the inguinal region, armpits, sides of trunk, and lumbar region. In others they are only seen on the extensor surfaces of the extremities; where they are limited to the back of the hands, the wrists or above the wrists, the elbows, knees, and dorsum of feet, and the extensor surface of the great toe, between its inner border and the tendon of the extensor longus hallucis. They appear from the first to the fourth day of the disease, and, if morbilliform, are very slightly if at all raised above the surface of the surrounding skin; they fade, sometimes before the eruption of small-pox appears, more frequently shortly after; but if they appear simultaneously with the characteristic eruption of small-pox they do not fade until after the lapse of from two to four days. They disappear on pressure and no staining results. The partial erythemas appear to vary a good deal in character and distribution in different outbreaks; but they are invariably followed by mild attacks.

II. *Hæmorrhagic Rashes.*—These are of two kinds—(1) Petechial, (2) Petechio-erythematous. They appear on the first, second, or third day of illness, are not attended by itching, but sometimes by a sensation of heat in the skin of the affected part, are not raised, and usually precede, but sometimes appear simultaneously with the characteristic eruption of small-pox.

(1) *Petechial Rashes.*—These are most frequently observed on the lower abdominal and inguinal regions—on an irregularly shaped triangular area, the base of which is formed by an imaginary horizontal line across the abdomen, sometimes at, sometimes above, sometimes below the umbilicus, the apex being in the middle line between the thighs four to five inches below the pubes. The sides of the triangle run outwards and upwards from its apex, parallel to, and three or four inches below, Poupart's ligament, to the great trochanter, and thence upwards to meet the base line. This is by far the most frequent site; but in some cases the rash extends on the lumbar region, and, in a more scattered form, up the sides of the chest; sometimes it is present in the axillæ, sometimes on the

neck, and on the chest under the clavicles; in others on the flexor surfaces of the joints. The rashes vary in colour with the varying proportions of the different petechiæ present, which are of two colours, bright brick-red and dark purple. The bright red petechiæ are small, round, or irregular in outline, vary in diameter from a point to a line, are rather deeper in colour at the centres than at the edges, and fade slightly, but do not disappear on pressure. The purple petechiæ, if seen when making their appearance, appear as minute purple dots which speedily increase in size till they are one to two lines across, and are round or irregular in outline with ill-defined margins. The two kinds of petechiæ are usually present together, imparting to the affected area a purple hue tinged with red. As the rash increases the purple tint becomes deeper, and the red petechiæ begin to fade. If the purple petechiæ be very thickly set at first, they coalesce and form large areas of a deep purple hue. In the abdomino-crural triangle above mentioned the purple petechiæ are usually most abundant along and just above and below Poupart's ligament, where they impart to the skin a deep purple, almost black colour; while the skin towards the margins of the triangular space remains of a mixed purple and red hue.

In some cases the bright red petechiæ only are present, and may cover the skin of the abdomen and lower part of chest, the flanks and lumbar region, or they may be limited to the groins and flexor surfaces of the joints of the extremities. If extremely abundant in these situations they impart to the skin the appearance of being covered by a punctate scarlet rash; but on pressure their petechial character is apparent because, while fading slightly, they do not disappear. In other instances the purple petechiæ only are present, and, as a rule, eruptions composed of these are less widely distributed than those composed exclusively of the bright red petechiæ.

There is another form of initial rash, not very often met with, that is indistinguishable both in distribution and in appearance from ordinary purpura, and therefore may be named "purpuric initial," to distinguish it from the "petechial initial." It consists of circular purpuric spots two to four lines in diameter, of the colour of ink or of the deepest violet, with well-defined margins and regular outline. This eruption has no preference for the flexor or extensor surfaces or the abdomino-crural triangle, but is distributed irregularly over the trunk and limbs, and is unaccompanied by any other initial rash. It occurs usually in children, is not accompanied by hæmorrhage from the mucous surfaces or elsewhere, and the spots are limited in number. The characteristic eruption of small-pox appears at the usual time.

(2) *Petechio-erythematous Rashes.*—These are formed, as the name implies, by a combination of petechial and erythematous eruptions. The erythema may be general, but is more often partial; it is frequently limited to the abdomino-crural triangle, sides of trunk, lumbar region, axillæ, neck, and flexor surfaces of limbs. It usually covers a larger area than the petechial portion of the rash.

When at its height the petechio-erythematous rash, if situated in the abdomino-crural triangle, presents a red, sometimes a deep red colour at the borders, deepening in colour towards the more central portions, where it often assumes a deep purple, almost black colour. The petechiæ are usually much more closely set at the central portions than at the borders. The skin is in most cases smooth, but in some it is faintly raised and rough, owing to the appearance of a few minute vesicles. Should the patient recover, the erythema disappears in a few days, but the petechiæ, especially the purple ones, fade slowly, leaving a brownish discoloration which, gradually changing to yellow, ultimately disappears completely.

The petechial and petechio-erythematous rashes reach their full development in about two or three days, are usually not raised and do not itch. When accompanied by hæmatemesis, hæmoptysis, hæmorrhages from the mucous surfaces and kidneys, and in women by metrorrhagia, they almost invariably foreshadow hæmorrhagic small-pox. The lighter the colour of the petechial portion of the eruption the greater is the probability of the attack ending in recovery, and conversely.

The Eruption.—The characteristic eruption of small-pox appears, as a rule, forty-eight hours after the onset of the initial symptoms; but there are many exceptions to this rule. In some cases a solitary papule appears on the face, hand, or elsewhere on the first day of illness, and is not followed by others until the usual time. In other cases numerous papules appear on the second day, followed by an abundant eruption on the third day, and occasionally the eruption does not appear until the fourth day of illness. The earliest papules are usually found on the face, arms, and back of wrists and hands, and are succeeded by others on the trunk and lower extremities. The bulk of the eruption on the lower extremities is often a day later in appearing than that on the face and upper extremities. In a number of cases it appears on all parts of the skin simultaneously; in others, first on the inner surfaces of the thighs, or on the nates. Simultaneously with its appearance on the skin, the eruption appears on the buccal mucous membrane, the tongue, hard and soft palate, fauces, and naso-pharynx; also on the vulva, sometimes in the vagina and in the lower part of the rectum. The eruption does not often affect the œsophagus, but is common in the larynx, and occasionally in the trachea as far as the bifurcation or a little lower. Sometimes a vesicle forms on the conjunctiva, but never on the healthy cornea. Bancroft has recorded a case in which old keratitis with pannus was present. Upon the vascularised portion of the cornea a small-pox papule occurred, which underwent the evolution characteristic of the specific lesion upon a mucous membrane.

The eruption is not distributed uniformly; as a rule it is most abundant on the face, scalp, extremities, and back, whilst the skin on the front of the chest is less affected, and the skin of the abdomen least. The eruption on the buccal mucosa, tonsils, and pharynx is often directly proportional to its abundance elsewhere. Generally speaking, it is less abundant on the flexor surfaces of the elbows and knees, and in the axillæ

and groins, than on the extensor surfaces. On the skin affected by petechio-erythematous rashes the characteristic eruption of small-pox is usually scanty, and it may be absent. In natural small-pox it varies in amount from a few hundred vesicles to tens of thousands; and if it be discrete the vesicles may sometimes be noted in groups of twos, threes, and fives. In small-pox modified by vaccination the whole of the eruption, in most instances, is out within twenty-four hours from the appearance of the first papule; but in natural small-pox, especially in confluent cases, the papules continue to appear until the third day of the eruption. It may frequently be noted that the eruption is more copious on areas of skin subjected to special pressure than elsewhere; for instance, round the waist in women, on the skin of the leg under the garter, on the shoulders of men under the braces, and also on areas where a local irritant has been applied before the appearance of the eruption, round varicose sores, and so forth.

Up to the appearance of the characteristic eruption the course of the disease and the symptoms are alike in natural small-pox and in small-pox modified by vaccination; but the evolution of the skin lesion in natural and in modified small-pox differs so markedly, the divergence of the symptoms is, in the main, so pronounced, that it is desirable henceforth to regard them as distinct diseases, and to devote separate consideration to each.

Natural Small-pox (or Variola).—The eruption of natural small-pox consists at first of minute bright red macules which disappear on pressure, and are neither hard nor raised. In the course of a few hours they increase in size, and are distinctly red, hard, and raised. The macule has now become a papule, and the stages of its growth from papule to vesicle, from vesicle to pustule,. and its desiccation, are as follows:—In the course of twenty-four hours the papule has swelled visibly, and on the second day shews distinct central vesiculation. The vesicle widens at its periphery day by day, at the same time filling out with serum, loses its redness, and at the fifth to sixth day of eruption has attained the limit of its growth. A full-sized vesicle is about one-fifth to one-fourth of an inch across, circular, raised well above the level of the skin, translucent, or of the colour of dull pearl, with rounded border, usually showing a shallow central depression, and its base encircled by a narrow but distinct zone of redness. It is filled with clear, transparent serum; on being pricked a small quantity of this exudes, but the vesicle does not empty, nor does its wall collapse. The central depression, or, as it is often termed, the umbilication, of the vesicle is invariably to be noted in a large number of vesicles, but not by any means in all. At the end of the fifth or on the sixth day of eruption the vesicle begins to become opaque. As the opacity increases the vesicle swells, losing at the same time its central depression, and acquires by degrees a dome shape; the surrounding areola becomes brighter, and in three, or at most four, days from the period of full vesicular growth—that is to say, on the eighth or ninth day of eruption—it presents a circular, dome-shaped

appearance, is completely opaque or yellow, is surrounded by a vivid areola, and has now become a pustule. On running a pin through it from side to side pus or turbid lymph escapes, and on forcibly emptying the pustule its wall collapses.

The papules of natural small-pox are red, raised, and hard. If the finger be firmly pressed on the skin and drawn slowly across it, the papules feel like small shot embedded in the skin. If the lesion, be it papule or vesicle, be gripped between the thumb and forefinger, it is felt to be in the skin, and when the vesicle has grown to some size its floor is indurated.

The mature vesicles vary much in size on any given area, some being considerably smaller than the typical size mentioned above; others, often on the back, being larger. Many vesicles when fully grown shew a narrow white ring at the periphery, with, in some instances, fine white strands radiating from the centre. When this white peripheral ring is present in a vesicular eruption it is usually regarded as diagnostic of small-pox.

The areola is present from the earliest stage of the vesicle, and is at its height on the eighth to the ninth day of eruption. It is brightest at its inner margin, shading off towards its periphery, is raised, and in the pustular stage is often more or less indurated. It begins to fade with the bursting and desiccation of the pustules.

The pustule, if it be not ruptured forcibly, remains intact for a day or more; then, if it rupture, usually in the centre, pus escapes, and, rapidly drying, forms a dirty yellow crust; if it remain intact it desiccates, forming a slightly raised, flat, brown prominence which falls off later. The majority of the pustules rupture.

From the first appearance of the macule the successive stages of papule, vesicle, and pustule with incrustation occupy about ten to twelve days. The crusts now begin to fall off, exposing a red surface which may be raised, flat, or depressed; in the last case it may or may not be ulcerated; or the crusts may adhere for a week or more unless removed by suitable applications. The unruptured pustules, by partial absorption or evaporation, become inspissated and of a brownish colour, this being especially noticeable on the palms and soles. The wall shrivels, and the pustule, losing its dome shape, becomes flattened; after a time its wall ruptures, and the dried contents and epidermis fall off together, exposing in some cases a raised, in others a flat, and sometimes a depressed, red epidermis.

Concurrently with the appearance of the skin lesion, eruption develops on the buccal mucosa, palate, tonsils, pharynx, and often also on the epiglottis, larynx, and trachea. At first small bright-red spots are seen which quickly increase in size. The central portion soon assumes a white appearance, and by the second or third day of eruption they shew as small roundish white spots of about the size of a millet-seed. When they have attained the limit of their growth on the third or fourth day they are smaller than the vesicles on the skin. Sometimes they

shew a narrow areola. There is often much swelling of the tonsils and mucosa generally. About the fifth day of eruption, or sooner, many of the vesicles rupture, exposing a ragged, ulcerated surface; this, if the eruption be confluent on the fauces and palate, has the appearance of dirty, disintegrating, diphtheritic membrane. The shreds of mucous membrane come away, the ulceration heals, the swelling of the parts subsides, and the throat resumes its normal condition about or before the time that the crusts are falling off the skin.

Although the evolution of the skin lesion of natural small-pox conforms to the description just given, the whole of the vesicles do not attain their full development simultaneously. Those that appear first maintain their lead throughout; and those on the face are, in point of development, usually a day in advance of those on the lower extremities; but on any given part of the body some vesicles are in advance of others, and later, while some of the pustules have ruptured and crusts are forming, some shrink, others desiccate unruptured, and a few abort. So that on the limbs, for instance, there can usually be seen dirty yellow scabs and brown, desiccated, unruptured pustules mixed together. On the face, however, most of the pustules burst. When the crusts have fallen off, and the ulceration healed, a branny or powdery desquamation follows, not only on the part of the skin covered by the pustule, but on the inner margin of the areolar area. If the pustules desiccate, unruptured desquamation often takes place on the areolar surface, sometimes before, sometimes after, the desiccated pustule has separated from the skin.

Symptoms.—The symptoms present in the pre-eruptive stage, headache, backache, pyrexia, and so forth, abate or subside completely when the eruption is fully out—in many cases even before the entire eruption has appeared.

In the vesicular stage, apart from the heat, itching, and discomfort due to the eruption, many patients are free from pain and fairly comfortable. But in severe cases with abundant eruption, deglutition may be painful or difficult, and there is generally laryngeal discomfort with husky voice and cough. Many patients are restless and sleepless; while noisy, violent, and sometimes crafty delirium may be noted, especially in confluent cases and in those with hæmorrhagic manifestations round or under the vesicles. As the vesicles approach the limit of their growth there is often considerable œdema of the skin, usually most marked on the face, neck, and limbs. About the sixth day of eruption, when the stage of pustulation begins, the temperature rises, febrile symptoms develop, the areola becomes wider and more vivid, the swelling of the skin increases, the vesicles, as they swell, assume a dull white colour, the central depression is obliterated, the surface, where the eruption is confluent, having the appearance of rough parchment. At the height of the pustular stage the vesicles have become yellow pustules, the areola being often deep red and slightly indurated, while the general condition of the patient becomes increasingly uncomfortable and painful. If the eruption be discrete, the dome-shaped yellow pustules, encircled by vivid red areolæ, stand out well

above the general level of the skin; but when confluent, the surface of the skin, covered with the closely set pustules, is more or less uniformly raised, except on areas where the distended pustules have coalesced and formed large bladders filled with pus. In the milder cases the swelling of the skin is usually moderate, but in severe attacks there is much subcutaneous œdema; the eyelids are often greatly swollen and can only be opened with difficulty, if at all; the nose forms a rounded potato-like protuberance; the great swelling of the lips and buccal mucosa causes the mouth to gape, with saliva sometimes trickling from it; the cheeks and neck are baggy; the contour of the face and neck almost obliterated, and the features so disfigured that the patient is not recognisable by his nearest friends. The extremities, the forearms, hands and feet especially, are much swollen and often acutely painful, the fingers being kept in a partially flexed position, while the weight of the bedclothes and the pressure of the mattress on the skin cause much discomfort and suffering. The tongue, mouth, and throat, swollen and covered with shreds of disintegrating mucous membrane and secretion, become dry and parched; there is great, often unquenchable, thirst, with, it may be, difficult and painful deglutition and offensive breath. The milder cases do not, as a rule, shew much restlessness or sleeplessness, and delirium is rare; but in severe cases these symptoms are pronounced, low muttering delirium is frequent, occasionally noisy and violent, and the constitutional symptoms are severe, with signs of increasing weakness and prostration. The voice is usually husky, the cough harsh and troublesome with embarrassed breathing in some cases, and often copious expectoration. There is usually little vomiting, large quantities of nourishment being retained. The bowels are generally constipated, but occasionally diarrhœa is present.

When the pustulation of the vesicles is mature—ninth or tenth day, usually a day or so earlier on the face and arms than on the lower extremities—the stage of incrustation begins. The pustules burst, and the oozing pus as it dries forms crusts and scabs, the areola fades, and the subcutaneous œdema subsides. There is pronounced fetor from the oozing pus, and the appearance of the patients is repulsive. By this time, or earlier in favourable cases, the faucial discomfort and distress will have lessened, and the urgency of the laryngeal symptoms subsided, though cough and expectoration are often troublesome. In favourable cases, as the process of incrustation proceeds the intensity of the symptoms of the stage of pustulation abates in some degree, sleeplessness being less marked, the mind less confused, and the temperature lower. But the patient begins to feel increasingly weak, often shewing very pronounced signs of physical prostration and exhaustion. In unfavourable cases the intensity of the symptoms increases, the pulse becomes exceedingly rapid, the temperature rises to 105° F. or 106° F., respiration is hurried and shallow, tremors and subsultus are marked, the sphincters are paralysed, the low muttering delirium merges into stupor, and the patient succumbs, usually between the ninth and fourteenth days of the disease.

With the completion of the process of incrustation—twelfth to

fourteenth day—the crusts and scabs begin to come away, but many adhere for a considerable time unless decrustation be hastened by suitable applications. As decrustation advances, though the skin is reddened, disfigured by crusts, ulceration, discoloured débris, and desquamation, the features become recognisable. In the absence of complications the patient now convalesces rapidly or gradually according to the severity of the attack. In the mild cases convalescence begins about the end of the second week; in confluent cases usually not till the middle or end of the third week, and then only in the absence of complications.

In some instances during incrustation the skin surrounding the pocks becomes reddened and inflamed, with the formation of bullæ of varying sizes. These burst and discharge their turbid contents, crusts form, and an impetiginous condition of skin results which is usually accompanied by pyrexia and constitutional symptoms, sometimes of considerable severity. The speedy removal of the crusts during the incrustation stage does much to prevent the occurrence of this condition. Septic erythemas, accompanied generally by a raised temperature, appear in some instances during the late pustular and early incrustation stages. The rash is usually patchy, affecting mostly the flanks, abdomen, and lower part of the chest, but sometimes its distribution is more general. In tint it may resemble measles, but hardly in other characteristics. In some cases an erythema resembling that of scarlet fever has been noted. Conjunctivitis, with or without muco-purulent discharge, is present in many—chiefly the confluent—cases, and not infrequently purulent ophthalmia occurs in infants and very young children. Other eye conditions arise which will be mentioned later (p. 512).

The *temperature*, which during the initial symptoms may have reached 104° F., or higher, begins to fall soon after the eruption appears; by the end of the first or on the second day of eruption it has fallen in discrete cases to 99°, or even to normal or subnormal; but in confluent cases it often does not fall much, if at all, below 100°. The remission continues in mild cases till the vesicles begin to be opaque, but in severe cases the period may be rather shorter. The temperature rises with the progress of pustulation. When this process is at its height discrete cases shew a temperature of 102° or 103°, rarely 104° F. In confluent cases it rises to 104° or 105°, and in fatal cases even higher. This is the so-called secondary fever of small-pox. The morning remissions are usually one or two degrees. The temperature falls gradually as the incrustation proceeds, and in uncomplicated attacks usually becomes normal between the eleventh and fourteenth days of the disease, according to the severity of the illness. If the skin lesions be deep, and septic manifestations or complications ensue, the pyrexia may persist for a considerable time.

In the early stage of eruption, with the fall of temperature, the *pulse* slows to 80 or 90; in mild cases even to normal; in confluent cases to 90 or 100. It remains slow till the pustular stage, then it becomes rapid, and in discrete cases is usually full and regular; but in confluent

attacks at the height of the pustular stage it becomes very rapid—120 to 130 or more, and visible pulsation of the carotids may often be noticed. In the pustular and incrustation stages it is often feeble and irregular.

Respiration is usually not much quickened in the vesicular stage, except in cases with marked laryngeal symptoms; but in severe cases in the pustular stage it becomes rapid, shallow, and often embarrassed.

Emaciation is not a feature of the milder forms of small-pox, but after severe attacks it is marked; if serious complications ensue, it may be extreme. The appetite returns in the milder cases as soon as the temperature falls; in severe and complicated attacks, more slowly. During convalescence many patients eat ravenously.

Modified Small-pox (or Varioloid).—Of the cases that occur in vaccinated subjects a large proportion is modified by vaccination. The evolution of the eruption is often so completely altered that it is difficult to recognise the identity of the natural and the modified diseases.

In modified small-pox the eruption, as a rule, is fully out within twenty-four hours of the appearance of the first papule, but sometimes not till later. Usually it is not very abundant. The macules quickly become papules, and many shew minute vesiculation at the end of twenty-four hours. The vesicles often attain their full growth in about three or four days. In size they are usually smaller than those of natural small-pox, more conical, perhaps less regularly circular, very often shewing a slight central depression only or none at all, and surrounded by a very faint red line. On the third or fourth day of eruption many of the vesicles become opaque, the lymph is cloudy, and, from the arrest of the process of pustulation at this time, they do not become pustules, but shrink and desiccate, the inspissated contents forming small, brown, flattish, slightly raised prominences about the size of a millet-seed under the horny epidermis. Those that become pustules attain the stage of full pustulation in about six days from the appearance of the eruption; they are usually smaller than the pustules of natural small-pox, more conical, surrounded by narrow areolæ, and often do not rupture. If they rupture, the contents form small, rounded, dirty yellow or brownish crusts of varying size, which in the course of a week or less fall off, exposing a flat, reddened, healed surface. The distinctive feature, therefore, of the eruption of small-pox modified by vaccination is that its evolution is hastened in all its stages.

Within a few hours of the appearance of the eruption in many cases, in others not until the eruption is fully out, the symptoms of the pre-eruptive stage subside and the temperature falls to normal. In some it rises a few degrees when the eruption is pustular, but in many it remains normal throughout the subsequent course of the illness. The constitutional symptoms are therefore of the mildest, and in many patients the disease, as far as regards subjective symptoms, is over when the eruption is fully out. In cases with a very abundant eruption there is often considerable swelling of the extremities and face, with œdema of the eyelids,

and perhaps considerable itching and discomfort for a day or two, but the intense irritation and pain noted in those suffering from severe natural small-pox are absent. In such cases there is some pyrexia and the appetite is impaired, but the speedy involution of the eruption in the pustular stage limits the duration and intensity of the symptoms, and the patient soon enters on convalescence, which is usually uninterrupted; with few exceptions no complications or sequels follow except a few boils, an occasional attack of mild facial erysipelas, slight conjunctivitis, or a small corneal ulcer. Recovery, except in rare instances, is rapid and complete, patients being with difficulty restrained from going out among the public before they are free from infection. Death, when it occurs, is usually due to some antecedent disease.

In both natural and modified small-pox *albuminuria*, with or without casts, is frequent, but usually is not very marked. It may occur in the initial stage, when pyrexia is high, and in patients with early hæmorrhagic manifestations, but more often it appears during the vesicular or pustular stages, and sometimes later. It may persist for a considerable time; but the signs associated with nephritis, such as diminished excretion and general œdema, are not often met with. Hæmaturia is often present in hæmorrhagic attacks.

In the severer forms of small-pox the lymphatic glands are generally perceptibly enlarged. The enlargement is observed, for the most part, in the inguinal and axillary, sometimes in the cervical, glands; it comes on during the vesicular stage, persists till the stage of incrustation, and then gradually subsides.

It is desirable now to proceed to the consideration of small-pox with special reference to the character and abundance of the eruption. With this in view it is convenient to form four groups or classes—viz., (1) **Small-pox without eruption**; (2) **Discrete small-pox**; (3) **Confluent small-pox**; (4) **Hæmorrhagic small-pox**—and to consider separately in each class the natural and the modified forms, bearing in mind that natural small-pox is not restricted to unvaccinated persons, but may occur in vaccinated subjects in whom the immunity afforded by vaccination has ceased. In regard to the confluent class, I include therein all cases with a moderate degree of confluence, usually styled semi-confluent small-pox, deeming it preferable to regard these as confluent cases of moderate severity, thereby avoiding unnecessary repetition.

Premising that the incubation-period, initial stage, and date of appearance of eruption are alike in these classes, I now proceed to a detailed description of each.

1. **Small-pox without Eruption.**—Occasionally such cases are seen. The initial symptoms are those already described, and may be either mild or severe, and may be accompanied by a partial initial erythema. At the time that the characteristic eruption should appear the symptoms subside, the temperature falls to normal, no eruption follows, and in a short time the patient is quite well. I have only seen such cases in vaccinated, and sometimes in revaccinated subjects; one such case

apparently communicated the disease to another person, who passed through an attack of modified small-pox.

2. **Discrete Small-pox.**—A. *Discrete Natural Small-pox.*—The full amount of eruption is out usually within twenty-four hours from the appearance of the first spot; on the fifth day of eruption (seventh of disease) the vesicles are of full size, encircled by a narrow areola; on the seventh to the eighth day of the disease commencing opacity is seen in many of the vesicles, and by the ninth day most of them are quite opaque, and those on the face are pustular, a bright areola encircling each. The pustules on the face rupture first, and small light or dirty yellow crusts form. On the extremities and trunk some rupture, others desiccate unruptured, and towards the end of the second week of the disease in many cases decrustation is proceeding and the patient enters on convalescence. The temperature usually falls to normal in the vesicular stage, rises a few degrees in the pustular, but is seldom higher than 101° to 102° F., though it may in some instances rise to 104°, and falls with the incrustation of the pustules. The pulse seldom exceeds 120. There is a good deal of swelling of the face and skin generally; and during the late vesicular and pustular stages the patient suffers pain and much discomfort from the eruption, and in addition there may be sore throat, due to eruption on the tonsils and neighbouring parts. The mind is sometimes confused, but delirium is very rare. In infants and children under three years of age the condition of the throat may cause them to take nourishment unwillingly. Lung complications are rare except in infants and children up to four years of age, in whom laryngitis, bronchitis, and, sometimes in the later stages, bronchopneumonia occur. Multiple superficial abscesses, erysipelas, cellulitis, septicæmia, transient facial paralysis, conjunctivitis or corneal ulcer, and otitis occur as complications, mostly in infants and young children, convalescence in those over five years of age being usually uninterrupted. Deep pitting occasionally results, but usually not, and there may be none at all. Death is usually due in infants and children to septicæmia, cellulitis, or to laryngeal and lung complications.

B. *Discrete Modified Small-pox.*—If the eruption be fairly copious the distribution is that described on p. 495. But if there be a comparatively sparse eruption, some pocks will usually be observed on certain areas of skin, viz. just above and between the eyebrows, the nose, the cheeks below the eyes, over the sacrum, above the patella, under the inner malleoli, and in the internal aspect of the instep. It is not abundant as a rule, and the number of vesicles may not exceed half-a-dozen; usually there are a few vesicles on the face, limbs, and trunk; but I have seen a case with only five vesicles all told, and these situated on the nape of the neck. Much of the eruption is slightly vesicular within twenty-four hours of its appearance, but in some cases the papular stage lasts for a couple of days before this happens. The course of the disease is short: the temperature falls to normal with the appearance of the eruption, and in very many cases does not rise again. In the mildest attacks the

patient feels quite well after the initial symptoms have subsided, and the disease, so far as regards subjective symptoms, is at an end.

In cases with a copious eruption the temperature rises to 99° or 100° F. during the pustular stage; the pulse is slightly accelerated, but the constitutional symptoms are very slight, the patient being convalescent within a week or ten days of the onset of the disease. It is free from danger to life, and convalescence, save for an occasional boil or rare attack of facial erysipelas, is usually uninterrupted.

In certain cases of modified small-pox some of the vesicles on the face, especially on the nose and cheeks, do not desiccate and fall off in the usual manner. The lymph appears to become partially organised, and a verrucose condition results.

Owing to the modifications produced in the characteristic eruption by vaccination, many forms of small-pox based on these modifications have been described, such as miliary, crystalline, acniform, and so forth; but the varieties are fanciful rather than important.

Marson described a variety based on the distribution and aggregation of the vesicles, which he named corymbose small-pox. Clusters of vesicles like corymbs appear on different parts of the skin, and the attacks were usually if not invariably fatal. This variety I have not seen.

Rare Forms of Discrete Small-pox, attended by Severe Nervous Symptoms.—Some attacks of discrete small-pox in vaccinated and unvaccinated subjects are ushered in by great mental disturbance, delirium, convulsions, and perhaps coma. In some cases these symptoms subside on the appearance of the eruption or shortly after; but in others there is no intermission of the initial delirium, which becomes more and more violent, and merges into acute mania that may last several weeks. If these symptoms subside the attack results in complete recovery; but permanent dementia may result. In other cases the coma of the initial stage becomes more profound, and the patient dies in a few days without regaining consciousness. In a few instances convulsions set in about the seventh to the ninth day of illness, coma rapidly supervenes, there is high temperature, and the patient dies in twenty-four to forty-eight hours. Only in very rare cases does recovery take place. The symptoms are usually due to congestion of the brain, and sometimes to hæmorrhage under the pia mater.

In very rare cases symptoms of great mental confusion, with loss of the power of co-ordination, occur in the initial stage, accompanied by aphasia, and, it may be, also by partial or complete paralysis of the extremities. Sometimes the patient is thought to be drunk. This state lasts a varying time, one, two, or three weeks; the patient then begins to recover the use of his limbs, and the power of articulation returns slowly, the utterance being difficult, thick, and jerky. The paralysis and loss of co-ordination last a very long time after the patient is convalescent, and his walk in many respects resembles that of tabes dorsalis. Time, however, brings gradual improvement; the general health is good, and the symptoms ameliorate if complete recovery do not take place.

3. Confluent Small-pox.—A. *Confluent Natural Small-pox.*—This includes all degrees of confluence, limited in some to small areas of confluent vesicles on the face and extremities; in others the skin of the face, neck, limbs, chest, and back is completely covered by vesicles, with often profuse eruption on the buccal mucosa, tonsils, and pharynx. In the former the eruption is fully out within twenty-four to thirty-six hours of the appearance of the rash, in the latter not until the second or in some cases third day of eruption. Shortly after the appearance of the eruption, the skin of the forearms and face often becomes deeply hyperæmic, in some uniformly erythematous; and as the vesicles grow their paler outlines are thrown into relief against the reddened background of skin. The temperature falls in milder cases to 99° F. or to normal, but in the severer not much, if at all, below 100° F. During the period of vesicular growth in milder cases the patient is free from restlessness, and, but for the heat, itching, and discomfort of the eruption, feels tolerably well. In severer cases, especially those in which the eruption is completely confluent on the face and extremities, there is frequent husky cough, some difficulty, it may be pain, in deglutition, with intense irritation of the skin and discomfort towards the end of the vesicular period. So acute is it that patients often tear the epidermis completely off their arms, legs, and face, exposing a raw oozing surface. The skin dries rapidly, becomes stiff, rough, and of a deep mahogany colour. In these cases the temperature rises to 104°-105° F., or higher; there is extreme restlessness, much delirium, rapid pulse, and the patient succumbs about the ninth or tenth day of the disease.

In the majority of confluent cases, as the vesicles approach their full growth, there is considerable subcutaneous œdema, most marked on the face, neck, forearms, hands, and feet. At the height of the vesicular period, and in the pustular stage, the eyelids are often intensely œdematous, the upper eyelid overlapping the lower; the patient is quite unable to open his eyes, and the lids can with difficulty be separated. Conjunctivitis with muco-purulent discharge is of frequent occurrence. The nose, cheeks, and lips swell enormously, the neck even in a greater degree; the hands and feet are swollen and acutely tender to the touch, the fingers being partially flexed. There is copious eruption on the buccal mucous membrane, fauces, and pharynx; the voice is husky, the cough harsh and troublesome, saliva trickles from the open mouth, and deglutition is painful and sometimes difficult. A day or two later pus oozes from freshly ruptured pustules and from under the recently formed scabs; there is much fetor, and the patient presents a picture of hideous disfigurement and helpless bodily discomfort without a parallel in acute infectious diseases. There is high temperature (103° to 105° F., or even higher), quick pulse, rapid breathing, cough and expectoration of mucus, fetid breath, unquenchable thirst, extreme restlessness, sleeplessness, and often delirium. In favourable cases, coincidently with the incrustation process, the subcutaneous œdema subsides, and the patient is able to open his eyes. As decrustation advances the features begin to resume their

normal outlines, and during the third week of the disease the patient generally enters on the stage of convalescence. In unfavourable cases, and these form 50 per cent of the confluent attacks, septicæmia sets in, the temperature rises to 105°-107° F., the pulse becomes rapid, weak, and irregular; the voice is husky, frequent cough with much expectorating, rapid, shallow breathing sometimes attended by dyspnœa, much fetor, muscular tremors, and sometimes diarrhœa come on; the urine and fæces are passed involuntarily, low muttering delirium is more or less constant, merging into stupor, and the patient succumbs usually from the tenth to the fifteenth day of the disease. If the patient survive till decrustation be well advanced, pleurisy, pneumonia—in children usually broncho-pneumonia—deep and extensive cellulitis, diarrhœa or other complication may supervene; and such complications often prove fatal.

A striking form of confluent small-pox deserves separate notice. In some of the completely confluent cases the vesicles at the usual period of full vesicular development (fifth to sixth day of eruption) are flat, with very shallow central depressions, only partially filled with serum not translucent, but of a doughy or pasty hue; there is not much, if any, subcutaneous œdema; the features, though blurred, are recognisable; the eyelids are not œdematous; there is little swelling of the face, hands, or feet other than that due to the confluent vesicular eruption; the skin is rough and flat, presenting the appearance of coarse parchment. The temperature ranges from about 100° to 102° F. in the vesicular stage to 104° or higher in the pustular stage; the pulse is rapid and weak, the mind is confused; there is great prostration, but not usually much discomfort. Keratitis, rapidly involving the entire cornea, often occurs. It is not accompanied by conjunctival injection or discharge. The first sign is a loss of corneal lustre followed by cloudiness and complete opacity. The whole cornea may become opaque in twenty-four to thirty-six hours from the onset of the condition; a portion or the whole of it may slough off in a day or two, and partial or complete anterior staphyloma result. The keratitis sometimes affects both eyes, but usually only one, or one less extensively than the other. This form of confluent small-pox is usually fatal, death taking place from the ninth to the eleventh day of the disease. Occasionally recovery takes place in patients between the ages of ten and twenty years, but it is slow and protracted, and there is much emaciation.

B. *Confluent Modified Small-pox.*—The course of the disease in this class of cases is precisely similar to that of confluent natural small-pox till about the third or fourth day of the eruption, when the vesicles have attained their full growth, being in most instances considerably smaller and more conical than those of confluent natural small-pox. But at this time a remarkable change in the evolution of the eruption takes place. Instead of the vesicles continuing to grow till the fifth day of the eruption, they shew on the third or fourth day a central opacity, or become uniformly cloudy, and by the fifth or sixth day are completely opaque; a few may become pustular, but the great majority shrink, and

desiccate unruptured, the skin being thickly studded with innumerable raised brown specks, about a line in diameter, more or less. At the height of the disease there is often great swelling of the face and neck, with marked œdema of the eyelids as well as subcutaneous œdema of the extremities; there may be some delirium, the temperature often rising to 100°-102° F. or more for a day or two. Concurrently with the desiccation of the eruption the subcutaneous œdema subsides, the temperature falls, and the patient about the eighth or tenth day of the disease, when natural small-pox is just at its height, enters on convalescence, which in most cases is uninterrupted except by the occurrence of boils. The vesicular, pustular, and desiccative stages are all shortened.

4. **Hæmorrhagic Small-pox.**—This includes cases in which cutaneous and subcutaneous hæmorrhages appear with or without the presence of the characteristic eruption of small-pox on the skin. It is convenient for descriptive purposes to divide these into two groups: the *first* includes those cases characterised by the presence of numerous cutaneous and subcutaneous hæmorrhages, by bleeding from the mucous surfaces and kidneys, by a complete or all but complete absence of the characteristic small-pox eruption, and are known as hæmorrhagic or black small-pox; the *second* includes those cases exhibiting, in addition to the characteristic eruption of small-pox, cutaneous and subcutaneous hæmorrhages, accompanied or not by bleeding from the mucous surfaces and kidneys, and are known as vesicular or pustular hæmorrhagic small-pox.

(1) *Hæmorrhagic or Black Small-pox.*—This is by no means rare. It occurs during both epidemic and non-epidemic periods. The majority of attacks occur in vaccinated persons. The initial symptoms are almost invariably severe, especially the backache; and there is often violent and long-continued vomiting, attended by severe epigastric pain. The temperature in the initial stage is not high, usually not above 100° F., often below it. Very early in the course of the disease the cutaneous and subcutaneous hæmorrhages appear. The cutaneous hæmorrhages may or may not be preceded or accompanied by either general or partial erythemas, which appear usually on the first or second day of the illness. If a general erythema be present it is often of a vivid red colour; the partial erythemas are of the character described under initial rashes. On the second or third day red and purple petechiæ may appear in masses in the groins, the flexures of joints, and elsewhere, with a general distribution of violet or ink spots elsewhere, to be succeeded by subconjunctival hæmorrhage in one or both eyes, usually beginning in the inner aspect of the eye, and gradually extending round till, if the patient live long enough, the cornea is encircled by a wide band of deep purple ecchymosis. Purple spots appear on the forehead and face; there are minute purple petechiæ on the eyelids, gradually increasing in size and number until the eyelids assume a blue-black appearance. Bruise-like patches, varying in size and situation, and suggestive but independent of contusion, not infrequently appear. Purple hæmorrhages may often be seen on the tongue, palate, and fauces, but the mucous membrane generally is pale. Blood oozes from

the gums, in rare instances from the skin, and epistaxis, hæmatemesis, hæmoptysis, and melæna may occur. Blood is passed in the urine, and in women from the vagina and uterus. The masses of hæmorrhage in the abdomino-crural triangle and other flexures get darker, and the violet spots increase in number. The temperature is usually low, seldom over 100° F.; often normal or even subnormal. The pulse is soft and compressible; the mind absolutely clear and unclouded. The breath is clammy, but there is no fetor. Nourishment is taken fairly, unless there is persistent vomiting. The patient is restless, and often complains of a sense of oppression in the præcordia. The backache is most severe and persistent. Retinal hæmorrhages sometimes occur.

As the disease progresses, sordes form on the gums; the skin of the face, dotted by purple and inky spots, becomes of an ashy hue, perhaps a little puffy, and the hæmorrhagic manifestations on the skin generally become more marked; the lips and tongue are blanched. In some cases a few scattered papules may perhaps be seen on close examination on the backs of the hands, on the dorsum of the foot, or on the forehead or cheeks; but in other cases not a single papule. In the great majority of cases the mind is unclouded to the last. Death may take place as early as the third, more often on the fourth, fifth, or sixth day, and is frequently due to sudden cardiac syncope.

In some cases no erythema is present, and there may be but a small number of large violet ink spots on the trunk and extremities, and a few smaller purple petechiæ, accompanied by epistaxis, hæmatemesis, blood in the urine, and metrorrhagia in women.

An exceedingly rare and rapidly fatal form of the black small-pox has been described in which the initial symptoms are most severe: the temperature reaches 105° F. or over, with delirium, coma, and collapse, rapidly terminating in death after an illness lasting a few hours. No skin hæmorrhages are seen, but internal hæmorrhages similar to those described on p. 488 are found. I have not myself seen this fulminant variety.

Black small-pox is invariably fatal. It rarely occurs in vaccinated subjects under the age of puberty. Young, vigorous, and apparently strong healthy adults form a considerable proportion of those attacked. I have not seen it in vaccinated subjects under seven years of age, nor in any one who had one-third of a square inch of well-foveated vaccination cicatrix and had also been successfully revaccinated. In unvaccinated subjects black small-pox may occur at any age.

(2) *Vesicular and Pustular Hæmorrhagic Small-pox.*—This class includes a very large number of cases occurring among vaccinated and unvaccinated subjects. There are two varieties—(A) Cases which, in addition to hæmorrhagic symptoms of varying intensity, shew a considerable amount of characteristic small-pox eruption; (B) Cases in which the hæmorrhage is confined to the cutis under the vesicle and into the skin immediately surrounding the vesicle, with or without hæmorrhages from the mucous membranes. These may be named sub- and peri-vesicular hæmorrhagic cases.

A. *Hæmorrhagic cases attended* by more or less abundant characteristic small-pox eruption.

Generally speaking, in this class a fairly copious eruption succeeds or accompanies the hæmorrhagic manifestations, the amount of characteristic eruption being usually in inverse ratio to the severity of the hæmorrhagic signs ; not only do hæmorrhages take place from the mucous surfaces and into skin free from eruption, but there is often hæmorrhage into the cutis under the vesicle, and into the skin immediately surrounding the vesicle. The temperature in these cases is usually about 100° F. in the vesicular stage, and if the patient live till the pustulation begins it often rises to 103°-104° F. The mind is always more or less confused, and there is often active and violent delirium, the degree of mental confusion and delirium being usually in direct ratio to the amount of characteristic small-pox eruption. The face and limbs swell in proportion to the amount of the small-pox eruption. The pulse is rapid, weak, and may be irregular. Respiration is quickened and shallow ; cough is usually troublesome. Albuminuria is generally present, and often hæmaturia. There is often much eruption on the mouth and fauces, while dried mucus adheres to the mouth, throat, and nostrils, and thirst is excessive. In fact the symptoms approach those of confluent natural small-pox.

Patients very rarely recover from this kind of small-pox. The duration of life is longer than in the pure hæmorrhagic, and shorter than in the natural confluent, cases ; it is directly proportional to the amount of small-pox eruption present, and in inverse ratio to the amount of cutaneous and other hæmorrhages. Death usually takes place from the seventh to the tenth day of disease.

B. *Sub- and Peri-vesicular Hæmorrhagic Cases.*—In these cases there is an absence of ordinary cutaneous and subcutaneous hæmorrhages. The eruption may be discrete or confluent ; the papules and line of redness round the vesicles are, however, often of a deep angry red, or even purplish colour. The vesicles develop in the usual way, but about the third day of the eruption a dark central discoloration appears in the vesicle ; it quickly enlarges, and, in twenty-four hours or less, the vesicle has a uniform purple or leaden appearance ; simultaneously with this change, if not before it, there appears round the base of the vesicle a claret-coloured areola, about a line in width, which does not fade on pressure. These sub- and peri-vesicular hæmorrhages may be co-extensive with the eruption. They are often seen on the lower extremities, especially on the legs ; in other cases on the lower and upper limbs and trunk, and in others on the face also. As the vesicles fill and are distended by serum, which is usually quite clear and free from blood or hæmoglobin, the sub-vesicular hæmorrhages disappear from view, but the clarety areolæ persist. There is sometimes hæmorrhage from the mucous surfaces and the kidneys, but this is not so marked as in the other variety of hæmorrhagic cases (Class A). There is often much fetor, great thirst, and usually delirium. Albuminuria is present in a large percentage of the cases. The temperature ranges between 99° and 102° F. in the vesicular

stage; and in the pustular rises to 103°-104° F., or even higher. The pulse is rapid and weak. Recovery is not infrequent, especially if sub- and peri-vesicular hæmorrhages be confined to the lower extremities, and to a few vesicles on the trunk or arms; but if the hæmorrhage be on the face, trunk and extremities, and the eruption confluent, recovery does not take place. I have seen a fatal case of discrete small-pox, with sub-vesicular hæmorrhage under every vesicle, but no purple spots or petechiæ, and no trace of hæmorrhage from mucous surfaces. Vesicular and pustular hæmorrhagic small-pox may be either confluent or discrete, but is most commonly confluent, and attacks both vaccinated and unvaccinated subjects.

Pseudo-hæmorrhagic Cases.—There is a form of small-pox sometimes called hæmorrhagic vesicular, in which the appearances are as follows:—No cutaneous or subcutaneous hæmorrhages penetrate either into the parts of the skin free from eruption or into the skin under the vesicles. About the fourth or fifth day the vesicles, when filling with serum, acquire a purple colour, tinged with red, due to the vesicular fluid being stained by hæmoglobin. The vesicle is usually well filled, and on being pricked reddish serum escapes. This is a totally different condition from the sub-vesicular hæmorrhage above described, which appears on the second to the fourth day of eruption, and disappears from view as the vesicle fills with clear lymph. In women some uterine hæmorrhage sometimes occurs. These pseudo-hæmorrhagic attacks occur in vaccinated subjects. Recovery is usual, and cases of this nature are sometimes recorded as recoveries from black small-pox.

Inoculated Small-pox.—On the second day after inoculation the skin at the points of inoculation is puckered, and of a yellow colour. On the third day a papule has formed; on the fourth a vesicle. On the sixth day, if inoculation has taken place in the arm, the axillary glands are swollen and painful, and on the seventh or eighth day the vesicle has become a pustule. The temperature is raised, and there may be headache, backache, and vomiting, followed soon—eighth to tenth day—by the characteristic general eruption of small-pox. Inoculated small-pox usually, but not invariably, runs a mild course.

Second Attacks.—These undoubtedly occur, but they are quite exceptional. Many small-pox patients state that they have had a previous attack, but if careful inquiry be made into the symptoms, distribution of eruption, and duration of illness, and the scars, if any, be examined, the alleged first attack will usually turn out to have been chicken-pox. In three-fourths of the cases of alleged second attack that have come under my notice, I was able to satisfy myself that the first attack had been one of chicken-pox; and in most of the others there was not sufficient evidence to shew whether the first attack had been small-pox or not. I have not seen a second attack in any one who bore unmistakable evidence of having had antecedent small-pox. The cases usually run a mild course like that of modified small-pox, but instances, in which the second attack was severe, are said to have occurred.

Small-pox after Revaccination.—In the majority of cases it will be found that the revaccination had been unsuccessful. Some persons who have been successfully revaccinated do, however, contract small-pox. Of cases observed by me the time intervening between the revaccination and the attack of small-pox varied from one to twenty-five years; the average being ten years. The attack is usually mild and modified, but I have seen a case of pure hæmorrhagic small-pox in a woman who stated that she had been successfully vaccinated four years previously; and on her arm were scars alleged to be due to and indistinguishable from those resulting from vaccination. I have not, however, seen fatal small-pox in any one whose primary vaccination shewed not less than one-third of a square inch of well-foveated scars, and who had also been successfully revaccinated.

Small-pox in the Fœtus.—This is said to have occurred as early as the fourth month. The liability of the fœtus to small-pox is not great, but it appears to increase directly with its age. It is, however, exceptional to find that infants born of variolous mothers, even during convalescence, have had small-pox in utero, or that they are suffering from it at the time of birth. Of half-a-dozen infants born of variolous mothers which have come under my observation only one had small-pox at the time of birth. But infants have been born at the full time who had evidently passed through an attack of small-pox in utero. Of the infants born of variolous mothers, some develop small-pox a few days after birth, having contracted the disease in utero; others contract it at birth, the eruption appearing at the usual time; and a few are insusceptible both to small-pox and to vaccinia. Cases have been recorded of infants with the eruption of small-pox well developed at birth, the mothers not having had small-pox; and in one such case the mother is said to have contracted small-pox from her infant.

Complications.—A number of complications arise in small-pox, many being due to pyogenetic infection from the skin and mucous membranes of the mouth, throat, and respiratory tract. As would naturally be expected, such complications occur much more frequently in severe than in mild attacks.

Skin and Subcutaneous Tissues.—Multiple superficial abscesses or boils are the most frequent of all complications. They are more common after severe than after mild attacks, and appear during or after the stage of decrustation; they are situated usually on the extremities, face, scalp, and back, vary in size from that of a large pea to a walnut, or larger, are unattended by much pain or constitutional disturbance, and are often present in large numbers. Large abscesses on the shoulders, hips, limbs, and neck are not uncommon. They are painful, often extend deeply, and are not infrequently accompanied by septic symptoms, which are sometimes very severe, and in rare cases death may result. Ischio-rectal abscess occurs occasionally. Gangrene, affecting isolated areas of skin, toes, scrotum, penis, and parts of skin subjected to pressure, occurs, but only in the course of severe attacks.

Cellulitis, usually affecting the extremities, supervenes in some confluent cases during the stage of decrustation. It may be widespread and extend deeply, sometimes involving a whole limb; the affected part is red, brawny, and hot to the touch; extensive sloughing of tissues may take place even if the part be deeply and freely incised; such cases often prove fatal.

Erysipelas is not infrequent; it comes on during the scabbing stage or later, mostly attacks the face and scalp, or the arms, and sometimes the scrotum; it is apt to spread, and is attended by pyrexia. When extensive, the constitutional symptoms may be severe, and the patient, if weakened by a severe attack of small-pox, is not unlikely to succumb.

Obstinate acne pustulosa of the nose and face is not uncommon during convalescence.

Eyes.—There is frequently much eruption on the eyelids and on the edges of the lids, accompanied with pronounced œdema. A vesicle rarely forms on the conjunctiva. When present it is small, being not unlike a phlyctenular ulcer. There is considerable conjunctival injection and swelling, with some lacrimation and occasionally muco-purulent discharge, the symptoms lasting about a week. Later in the disease phlyctenular ulcers are not infrequent. Conjunctivitis is present in a large proportion of confluent, and in a small proportion of discrete cases; it occurs mostly during the vesicular and pustular stages, but sometimes during convalescence. In adults and children over four years of age it is not usually severe, and subsides under suitable treatment. But in unvaccinated infants and children under four years of age it is not infrequently attended by profuse purulent discharge, with swelling of the lids, the upper so overlapping the lower that it is with the utmost difficulty that they can be opened. In favourable cases it yields to treatment, but in others corneal ulcer develops, or keratitis sets in followed by sloughing of the cornea, partial or complete anterior staphyloma resulting. Simple corneal ulcer occurs not infrequently; it usually yields readily to appropriate treatment.

A peculiar form of corneal ulceration is sometimes met with. It is quite superficial, begins at the margin of the cornea, gradually creeps from one side to the other, and denudes the cornea of its epithelial layer. It is accompanied by pain, photophobia, and injection of the corneal zone of vessels and of the conjunctiva; infiltration of the deeper layers of the cornea does not occur. As the ulceration progresses the renewal of the epithelium follows on closely, the ulceration shewing as a thin line as it creeps from one side of the cornea to the other.

Keratitis is of fairly common occurrence, especially in confluent cases. It affects adults as well as children, but the latter more, in proportion. Rubbing of the face on the pillow, especially in children with confluent eruptions, leads to removal of the epidermal covering of the vesicles on the lids, so that the lids become hard and stiff, and very often keratitis follows soon. It sometimes occurs in the late vesicular, but more often

in the pustular and incrustation stages. It usually affects one eye, or if both eyes, one less severely than the other. Photophobia and increased intra-ocular tension are generally present; as a rule the inflammation begins at the outer margin, and is often limited to one-half of the cornea; it is sometimes accompanied by hypopyon, in other cases by sloughing, and formation of a deep perforating ulcer. If the ulcer be not very deep, the opacity often disappears in time, though it is sometimes permanent. The whole cornea may, however, be involved, in which case there is great danger that the sight of the eye affected will be lost. In keratitis occurring during the course of confluent attacks, especially those in which the vesicular eruption is flat and pasty in appearance, there is often complete absence of injection of vessels of the conjunctiva, or of the corneal zone, and no photophobia or lacrimation. The first sign of its onset is diminished lustre of the cornea, which looks dull and sluggish; it quickly becomes cloudy, and the whole cornea may become opaque in from twenty-four to thirty-six hours. In a day or two it sloughs, discharge of the aqueous humour follows with prolapse of the iris, protrusion of the lens, and complete anterior staphyloma; or even panophthalmitis may ensue. In other cases only a portion of the cornea sloughs, and if the perforation be small, a small staphyloma only results. This form of keratitis is often limited to one eye, but if both be affected, one usually suffers less than the other. Blindness due to small-pox usually arises from keratitis, sometimes from deep corneal ulcer.

Retinal hæmorrhage occurs in some hæmorrhagic cases. Iritis is occasionally seen; cyclitis, choroiditis, and retinitis are very rare. Orbital cellulitis is met with in a few cases.

Otitis media is uncommon, occurring usually in children with severe attacks during the stages of pustulation and desiccation. Sometimes, though rarely, facial paralysis follows; mastoid abscess is very rare.

Respiratory Tract and Lungs.—Nasal catarrh is rare, and only occurs in a very few confluent cases. Epistaxis and hæmoptysis are seen in hæmorrhagic small-pox. Laryngitis is usually caused by the presence of vesicles on the mucous membrane of the larynx: it occurs in vesicular or pustular stages in a large number of confluent and occasionally in discrete cases. Its onset is usually gradual, and is attended by husky voice, laryngeal cough, and not infrequently by dyspnœa which may render tracheotomy or intubation necessary. Immediate relief is often thereby obtained, but unless the patient be young, and the attack of small-pox not very severe, recovery seldom takes place. Most confluent cases with laryngeal obstruction have bronchitis, and many exhibit signs of hypostatic pneumonia, sometimes of bronchopneumonia. Ulceration of the larynx with necrosis of cartilages occurs in a few cases. Œdema of the glottis is comparatively rare. Bronchitis is always present in severe cases, being attended by frequent cough and much expectoration. In unvaccinated children, bronchopneumonia is not infrequent, very often proving fatal; in adults it is less common. Pleurisy with suppurative

effusion and lobar pneumonia occur occasionally in severe attacks, for the most part during the stages of incrustation and decrustation.

Digestive System.—Glossitis of varying severity occurs in the vesicular or pustular stages of confluent cases. When severe it is attended by much pain; the tongue is often enormously swollen, fills up the cavity of the mouth, protrudes from the lips, and prevents the patient taking nourishment. Glossitis, if severe, is usually a fatal complication. Parotitis is not uncommon, in some cases ending in suppuration.

Ulceration of the palate, fauces, and pharynx, attended by a ragged condition of the mucous membrane due to rupture of the vesicles, is not infrequent; and if the eruption be very copious, the fauces and tonsils appear to be invested with dirty disintegrating diphtheritic membrane; the condition resembles but is not diphtheria. Diphtheria is very rare in small-pox. Ulcerative stomatitis occurs, but gangrenous stomatitis is rare. Pharyngitis is usual in patients with much eruption in the pharynx; post-pharyngeal abscess is of rare occurrence.

Heart and Blood-vessels.—Myocarditis is present in a large number of severe cases. Pericarditis and infective endocarditis are extremely rare. Phlebitis, usually of the lower limbs, is of infrequent occurrence during the stage of incrustation or later.

Abdominal Viscera.—Peritonitis is uncommon. I have seen it, in an adult male, associated with pleurisy; in another case it was limited to the left hypochondrium and to the epigastrium, the spleen being studded with large infarcts, and in two cases after abortion. Abscesses in the liver and kidneys have been recorded, but are exceedingly rare. Infarcts are sometimes found in the spleen. Albuminuria is frequent, but nephritis is uncommon; I have seen the latter during convalescence. Cystitis occurs occasionally.

Septicæmia appears in many confluent cases during the stages of pustulation and incrustation, and later in cases complicated with deep abscesses and extensive cellulitis. Pyæmia occurs occasionally, and is sometimes associated with acute infective changes in some or all of the principal joints.

Rheumatism is exceedingly rare, but may occur in convalescence. *Orchitis*, often double, with effusion into the tunica vaginalis occurs, and usually in the pustular and incrustation periods. *Ovaritis* I have not seen, but it is said to have occurred. *Phimosis* and *paraphimosis* are sometimes seen in children. *Cellulitis of the scrotum*, sometimes involving the penis, comes on in some severe cases during the second or third week. The parts are painful and tender to the touch, intensely red, hard, and much swollen. In extreme cases sloughing of the tissues takes place.

Nervous System.—This is perhaps more often involved in small-pox than in the other acute eruptive infectious diseases. The nervous manifestations appear during any stage of the attack, usually develop rapidly, and may originate in the brain, spinal cord, or peripheral nerves, the spinal cord being more frequently affected than the brain.

Initial Stage.—The intense headache is not infrequently attended

with delirium, which usually subsides when the eruption has come out and the pyrexia abated; but in some instances, of which I have seen one, it merges into acute mania. In the vesicular hæmorrhagic form it is often continuous and violent from the first, and only ceases with the death of the patient; in others there is some remission during the vesicular stage, with exacerbation when pustulation begins. Convulsions not infrequently occur in children in the initial stage; coma of varying intensity, with which may be associated paralysis, either general or affecting the extremities only, is present in some instances. In others a mental and ataxic condition similar to that caused by alcohol occurs, and patients shewing such symptoms in the initial stage of small-pox have not infrequently been thought to be drunk. The coma usually passes off during the vesicular stage, but the paralysis may not, and is often long continued; should recovery take place, gradual improvement begins during convalescence, but some die in the acute stage of the illness. Hallucinations and melancholia are sometimes noted.

Eruptive and later Stages.—In addition to delirium and the occasional continuance of the early coma and paralysis, acute mania may develop during the eruptive stage; some recover, but others become permanently insane. In one case, an adult male under my care, with exceedingly mild modified small-pox, no remission of the delirium of the initial stage took place, and it merged during the vesicular period into violent mania lasting about a fortnight; the acute condition gradually abated, ultimately resulting in harmless dementia, and after three months' detention in the hospital, he was removed to a lunatic asylum. The post-febrile insanity of small-pox is sometimes associated with paralysis.

Of the graver forms of paralysis incidental to small-pox, *paraplegia*, of which a considerable number of instances have been recorded, is the most serious and generally proves fatal. It usually appears in the pustular stage, or later, during early convalescence, is generally accompanied by paralysis of the sphincters, and may follow either mild or severe attacks. In a patient, a female of eighteen years of age, under my care, it occurred on the fourth week, during early convalescence from an attack of discrete natural small-pox, and proved fatal. *Hemiplegia* is much less frequent than paraplegia, and the outlook as regards recovery is much more hopeful. Aphasia may develop concurrently with hemiplegia or independently of any associated paralysis, and lasts in either case a considerable time, usually, however, ending in recovery. Facial paralysis may or may not be associated with otitis media. *Peripheral neuritis* is very rare, is usually limited to circumscribed areas, and may be associated with paralysis and permanent atrophy of special muscles. One or two instances of *acute ascending paralysis* have been recorded, and one case of meningitis; all being fatal. Cerebral and nervous complications are met with in both modified and natural small-pox, and occur in mild as well as in severe attacks. *Cerebral hæmorrhage* is very uncommon. I have seen two instances in adults at an early period in the stage of pustulation; both

proved rapidly fatal, the hæmorrhage being one-sided and large. The patients had severe attacks of small-pox, one being of the vesicular hæmorrhagic type.

Aldrich has recorded a case of profound *neurasthenia* following severe small-pox. He has also collected particulars of fifteen recorded instances of *disseminated encephalo-myelitis.* The cases exhibited ataxic movements of the extremities, usually most marked in the legs, slow and awkward movements, slow monotonous and jerky speech, faulty articulation, a varying degree of mental degradation, and the symptoms shewed a decided tendency to improve.

Pregnancy.—Liability to abortion increases directly with the age of the fœtus and the severity of the attack of small-pox. In hæmorrhagic and severe confluent cases abortion invariably occurs if the patient survive long enough; in the former, not infrequently during the initial stage, in the latter usually during the vesicular stage. It is often attended with much hæmorrhage, and sometimes the placenta is retained. All the hæmorrhagic and nearly all the confluent cases die. In discrete natural small-pox abortion is much less frequent and the prognosis is hopeful; in modified small-pox it occurs in, perhaps, about a third of the cases, recovery being usual. In the discrete natural and in the modified diseases, abortion usually takes place during the second or third week of the disease, sometimes during convalescence, or even later.

Sequels.—*Pitting.*—In cases in which the skin lesion is superficial the pitting is slight or absent. At first, on the separation of the desiccated scab, there is often considerable hypertrophy of the papillæ at the site of the pustule, the epidermis being reddened and raised. In course of time this subsides and leaves the skin quite smooth or faintly pitted. But in cases in which the skin lesion is deep and followed by ulceration, the pitting is marked and sometimes excessive, being most noticeable on the face, which sometimes presents a ragged verrucose appearance. The extent and depth of pitting are in direct ratio to the depth of the destructive inflammation of the papillæ of the skin. In a few confluent cases in which there is destructive inflammation of the corium followed by deep suppuration and abscesses, bands of cicatricial tissue form, and a *cheloid* condition results. The face, which is the part usually affected, becomes scarred and disfigured; distortion of the eyelids, nose, mouth, and cheeks may result in much facial disfigurement. I have seen an extreme instance of this, the patient being so disfigured that he was unable to find employment for a long time after his recovery.

Alopecia is noticeable only after severe attacks, and is usually more marked in adults than in children. If the depth of the lesion be such as to destroy the hair-follicles, permanent partial, sometimes almost complete, alopecia follows. But in many cases the hair grows again in great abundance. The nails are sometimes shed.

Pigmentation.—When the desiccated scabs fall off there is in all cases a red discoloration which lasts a considerable time. In vesicular and pustular hæmorrhagic cases there is dark pigmentation of skin, usually

most marked on the lower extremities. This pigmentation lasts a long time and disappears very slowly.

Tuberculosis of the lungs occasionally follows a severe attack of small-pox either during convalescence or later, but it is a rare sequel.

Convalescence lasts a varying period—from a week in the mildest case to many months in the most severe; a few patients never completely regain their health. But in most cases ultimate recovery is complete, and it is not an unusual occurrence to hear patients assert long after recovery from severe small-pox that they enjoy better health than before. Recovery from discrete and mild confluent small-pox, unaccompanied by hæmorrhagic symptoms, whether in vaccinated or unvaccinated subjects, is in almost every case rapid and complete. Recovery after severe confluent and vesicular and pustular hæmorrhagic attacks is usually slow, and is often retarded by the occurrence of serious complications.

The **duration of the infectious period** is so variable that a hard and fast rule as to its limits cannot be laid down. It varies from a week in the mildest to two months or more in very severe cases. In discrete cases with abundant eruption it lasts usually three to four weeks. Under the thick epidermis of the palms of the hands and the soles of the feet, and under the nails, many of the pustules do not rupture, and must be cut out.

A small-pox convalescent should not be allowed to go out in public until the medical man has satisfied himself, by personal observation, that the whole of the skin is free from crusts, desiccated unruptured pustules, and powdery débris.

The co-existence of small-pox with other acute infectious diseases, each in the acute stage, is very rare indeed. In observations spread over a series of years, including many thousands of cases, I have only seen a few cases of concurrent small-pox and whooping-cough; two cases with membrane in the larynx, and one with membrane in the trachea, the membrane being similar to that of laryngeal and tracheal diphtheria. Most of the recorded cases of co-existence of small-pox with scarlet fever and with measles are instances of scarlatiniform and morbilliform initial rashes. Welch and Schamberg record a case of concurrent small-pox and chicken-pox. Of course one or other of the acute infectious diseases may occur in small-pox patients during the stage of decrustation and during convalescence.

Erysipelas occurs in the incrustation and convalescent stages of small-pox, but I have not seen it in the acute stage.

Diagnosis.—Difficulties occur, first, in the initial stage; second, in the eruptive stage; and it is not possible, until the initial symptoms have been followed by the characteristic eruption, to make a positive diagnosis of small-pox. Nevertheless, even in the initial stage, if due weight be given to certain symptoms, some approach to a correct diagnosis may be made. Should a person be suddenly seized with headache, severe backache, rigors, epigastric pain, nausea with or without

vomiting, and complete anorexia, and should these symptoms be accompanied by high temperature, rapid pulse, and (though not at first) much prostration, the onset of small-pox may be strongly suspected. If, in addition to these symptoms, on the first, second, or third day a petechial erythematous rash appear on the abdomino-crural triangle, with or without its appearance on other flexor surfaces, one may say, almost with certainty, that the disease will prove to be small-pox. A trustworthy history of definite exposure to the infection of small-pox within the usual limits of the incubation-period would materially increase the probability of the case being small-pox. But the probability is increased to certainty if on the second or third day of illness there appears an eruption of red macules on the face, extremities, and, to a less extent, on the trunk, which soon after their appearance are raised, distinctly hard and "shotty."

A. *Diagnosis in the Initial Stage.*

In its initial stage small-pox counterfeits certain acute infectious and other diseases, notably scarlet fever, measles, typhus, syphilitic roseola, influenza, erythemas, German measles, lumbago, copaiva eruption, and menstrual rashes.

Scarlet Fever.—The symptoms common to small-pox and scarlet fever are headache, nausea or vomiting, anorexia, rigors. The pyrexia is of varied degree, the pulse is rapid, respiration is quickened, and in both the skin may be dry.

Symptoms peculiar to scarlet fever.—The patient usually complains of sore throat. On examination a bright red ring of injection is seen on the uvula and free edge of the soft palate and pillars of the fauces; and there may or may not be inflammation of the tonsils with dots of exudation in the crypts; perceptible enlargement of the cervical or submaxillary glands is present in many cases; the tongue is coated by a white fur, the swollen papillæ showing red on a white ground.

Symptoms peculiar to small-pox.—Severe backache, absence of scarlet injection or inflammation of the fauces such as is usually present in scarlet fever, no enlargement of the cervical or submaxillary glands. The throat may feel dry, but is not sore. The tongue may be coated, but its papillæ are not enlarged. In most cases of small-pox the temperature is higher than in scarlet fever; but in hæmorrhagic small-pox with scarlatiniform initial rash the temperature is often low.

If the initial erythema of small-pox be general, enveloping the skin of the face, neck, trunk and limbs, it resembles the rash of scarlet fever; but on looking closely it will be noticed that the punctate appearance, which is always present on the thighs and arms in the case of bright scarlet rashes, does not appear in the initial erythema of small-pox. In the groins there will most probably be a more marked deepening of the tint of the rash than is to be noticed in scarlet fever. It may, however, be impossible to arrive at a diagnosis from the appearance of the eruption. The fauces should therefore be examined. In a case of scarlet fever with an eruption so extensive and bright there will be marked redness of the

faucial ring and tonsils, with probably some swelling of the latter. There may be some reddening in small-pox, but the characteristic appearances of scarlet fever will be absent.

If the erythema be partial, limited to the trunk alone, or to the trunk and flexor surfaces of the limbs, scarlet fever may be excluded by the absence of eruption on the neck and upper part of the chest, by the absence of faucial injection, and of cervical and submaxillary glandular enlargement. The rash of scarlet fever is usually brighter in tint than the scarlatiniform rash of small-pox; further, in a large number of cases this difficulty in the diagnosis will not arise if it be remembered that these initial scarlatiniform rashes do not occur in children under ten years of age. Partial initial scarlatiniform erythemas present perhaps less difficulty in diagnosis than general scarlatiniform erythemas.

The eruption of scarlet fever, however, occasionally counterfeits the initial petechio-erythematous rash of small-pox so closely that a mistake in diagnosis may readily occur. In such cases, along with typical scarlet inflammation of the fauces and enlargement of the submaxillary and cervical glands, there is a brilliant scarlet rash, with minute purple petechiæ shewing on the neck, just above the clavicles, and in the groins. It is most necessary that particular care be taken to weigh well the significance of the faucial inflammation and cervical and submaxillary glandular enlargement that are invariably to be noted in these cases; because the minute purple petechiæ in the groins and on the neck are indistinguishable from those that appear in these situations in cases of hæmorrhagic small-pox with a general bright scarlatiniform initial rash. After examining the throat there should be no difficulty as to diagnosis.

Measles.—Symptoms common to measles and small-pox are—eruption, pyrexia, rapid pulse, anorexia, and in some cases suffusion of the conjunctivæ.

In measles the catarrhal symptoms—lacrimation, cough, coryza—are usually present from the first, and Filatow's or Koplik's spots will be seen on the buccal mucosa, unless, as sometimes happens, they have disappeared shortly after the eruption has come out. The eruption appears on the skin usually on the third or fourth day; it consists at first of minute, raised, pink dots behind the ears, on the forehead, chin, cheeks, and neck, rapidly shewing on the limbs and chest. Measles mainly attacks children under ten. The eruption reaches its height on the second or third day of the rash, that is, on the fifth or sixth day of the disease; it is then composed of large, soft, velvety, raised, pink papules, confluent in many parts of the skin. On drawing the fingers across the forehead, the spots, although very distinctly raised and somewhat resistant, are soft and velvety, not hard or shotty. The temperature in measles is not usually high until the rash appears, and it reaches its height with the full development of the eruption.

In small-pox with initial morbilliform eruption some of the usual initial symptoms will be present, but there will be an absence of Filatow's spots and catarrhal symptoms, though possibly there may be some

conjunctival suffusion. The initial eruption appears on the first or second day of illness on the face, trunk, and extremities simultaneously. The spots at first are larger in size than the minute spots of measles, and the eruption has spread over the entire surface of the skin by the time that the eruption of measles is beginning to appear on the face and neck. The eruption is very slightly if at all raised. It disappears in twelve to twenty-four hours after it has reached its height, and does not leave the faintest stain. Before, simultaneously with, or immediately after the disappearance of the rash the papules of small-pox appear and the temperature falls. If the initial morbilliform rash be partial it appears on the groins, sides of the trunk, the flexor surfaces, or the extensor surfaces of joints; it is not accompanied by catarrhal symptoms; and having regard to its distribution, should not give any excuse for a diagnosis of measles. In a very small number of cases of measles, on the first or second day of the disease, an initial general erythema occurs which is absolutely indistinguishable from the general scarlatiniform erythema of small-pox. It is seen, however, so far as my observation goes, only in children under ten, the age period in which, as far as I know, the initial scarlatiniform rash of small-pox does not occur.

Typhus.—Symptoms common to typhus and small-pox are pyrexia, headache, rigors, anorexia, thirst. In typhus there is occasionally an initial erythema on the face and forearms on the third or fourth day, followed by the typhus eruption of red macules on the forearms, chest, abdomen, and limbs on the fourth to the fifth day. Hardly ever does the eruption of typhus appear on the face. The macules are not in the faintest degree hard or raised. In small-pox the characteristic eruption has appeared, as a rule, by the third or fourth day of illness, and with its appearance, or shortly after, the high temperature and initial symptoms subside; whereas in typhus the temperature is continuous.

Syphilitic Roseola ("Macular Syphilide") appears usually on the trunk and face, soon changing to a raw-ham colour; it is not accompanied by initial symptoms of the severity of small-pox, unless it appear just after a debauch, when headache and malaise will doubtless be present. The inguinal, perhaps the cervical lymphatic, glands will be found enlarged.

Influenza.—Considerable difficulty may be experienced in the diagnosis of small-pox and influenza on account of the close similarity of the initial symptoms of the former disease to the symptoms of the latter. The non-appearance of the characteristic eruption of small-pox on the third day will solve the difficulty.

Erythemas—In many cases neither the initial symptoms nor the initial temperature of small-pox are present. Erythemas, due to shell-fish, etc., may present considerable resemblance to small-pox initial rashes, not only in their appearance, but in the rapidity of their development. If there be no headache or backache, and the temperature not much raised, inquiry should be made as to the recent diet of the patient. In many instances the cause of the attack may thereby be discovered. In most

cases of food poisoning the onset of the symptoms is more sudden than even in small-pox.

Erythema Multiforme.—When neither the initial symptoms nor pyrexia of small-pox are present there should be no difficulty in diagnosis. But erythema multiforme is sometimes accompanied by high pyrexia and symptoms closely resembling those of small-pox. In such cases it is desirable to inquire if there is any history of rheumatism—perhaps the patient may have had an attack of that disease, or have had a similar rash and symptoms before. Should a history of rheumatism be elicited, it would be advisable to wait until the appearance or non-appearance of the characteristic symptoms of small-pox solve the difficulty.

In *German measles* the initial temperature and symptoms of small-pox are absent.

Copaiba Eruption.—In this there is usually an absence of the initial symptoms and temperature of small-pox.

Lumbago has been mistaken for small-pox, but the absence of fever, of headache, and other symptoms should be sufficient to exclude the diagnosis of small-pox.

Menstrual Eruptions.—A general erythema, covering the entire skin, of a deep purple colour, and fading on pressure, occurs sometimes in women at the climacteric age. The colour is so dark that it has sometimes been mistaken for hæmorrhagic small-pox. Small-pox should be excluded, without much difficulty, because the mucous hæmorrhage is exclusively uterine, there being no bleeding from the gums, epistaxis, hæmoptysis, hæmatemesis, nor any purpuric spots on the skin. The eruption is not accompanied by the initial symptoms of small-pox, except perhaps back-ache, nor by the prostration that invariably attends the hæmorrhagic small-pox.

B. *Diagnosis in the Vesicular Stage.*

Small-pox, when the characteristic eruption is fully out, may be mistaken for diseases that are accompanied by papular, vesicular, or pustular eruptions. These are chiefly measles, chicken-pox, syphilis, eczema, enteric fever, bromide and iodide eruptions, prickly heat, acne, herpes, lichen, glanders, and rheumatic rashes.

Measles.—Confluent small-pox, on the first or second day of the eruption, is frequently diagnosed as measles. The signs that mislead the observer are usually confined to the face and arms, where the skin is often congested, intensely hyperæmic, of a purplish-red, studded with large raised papules about the size of the spots of measles. The skin is swollen as in measles, the eyes are most probably suffused, and a careless observer not looking closely may easily be mistaken as to the nature of the disease. In small-pox, however, careful examination will shew that the papules are more raised than those of measles, that minute vesicles are forming in the centre of some, if not in many, of the papules, and on pressing the fingers firmly to the forehead and drawing them slowly across, the papules are felt to be resistant, hard, and "shotty." In measles there is not a trace of vesiculation, and the eruption, though

resistant, is velvety and soft—not in the faintest degree indurated. Further, on examining the mouth and throat numerous small white spots of the size of a sago-grain or larger will be seen on the tongue, tonsils, pharynx, and buccal mucosa if the case be small-pox. But if measles, the small white Koplik's spots, if present, will be seen mostly on the buccal mucosa opposite the molar teeth, not on the tonsils or pharynx.

Chicken-pox is the disease most commonly mistaken for small-pox, and cases of small-pox in unvaccinated children are very frequently mistaken for chicken-pox. The diagnostic points of chicken-pox are as follows:—

(i.) Initial Symptoms.—There is usually complete absence of these in chicken-pox, but occasionally, and mostly in adults, they closely simulate those of small-pox, except that

(ii.) The temperature is not at all or only slightly raised before the rash appears, and may or may not rise when the rash comes out; but if it be raised before the appearance of the rash it does not then fall.

(iii.) Distribution of Eruption.—The eruption is most abundant on the trunk and sometimes on the scalp; it is less on the face, less still on the arms, thighs, forearms and legs, and least of all on the hands and feet. It is almost invariably discrete, although it may be so abundant as to be nearly confluent, and may appear all in one crop, or in successive crops, extending over one, two, three, four, five or more days after the first.

(iv.) Character of Eruption.—In all cases of chicken-pox the eruption is at first either macular or papular; but, on account of the absence of symptoms, the eruption is not usually observed until it has reached the vesicular stage. When there is a fairly copious eruption, some of the vesicles are round, others oval, the latter being usually in the axillary folds and flanks, with the long axis of the oval parallel to the folds of the skin. But if there be a very sparse eruption, not infrequently all the vesicles are round. The vesicle of chicken-pox is more superficial than that of small-pox, and its floor is very slightly indurated as long as the vesicle remains intact. On the forearms, hands, legs, and feet, the vesicles are usually round, and often less superficial than on the trunk. Some of the vesicles mature, often within twelve, always within twenty-four, hours of their appearance. No such rapidity of evolution characterises the small-pox vesicles. When mature, they are shiny, translucent, and filled with clear serum; if transfixed and pressed, the contents escape and the vesicular wall collapses. The vesicles rarely shew a central depression until after rupture, which frequently occurs as soon as the vesicle is mature. When rupture takes place either a little serum escapes, with consequent partial central collapse of the wall of the vesicle, and a central depression results, or all the serum escapes, a flattened empty vesicle resulting.

In small-pox the initial symptoms are marked and the temperature is high, falling when the eruption is fully out. The lesion lies deeper in the epidermis than that of chicken-pox, and it is not fully vesicular within twenty-four hours of its appearance, either in natural or modified

small-pox. When mature, the vesicle often shews a central depression and a narrow white ring at its periphery, and can only be emptied by cutting it open.

Apart from such help as may be obtained from a consideration of the initial symptoms and temperature, the differential diagnosis of chicken-pox and small-pox rests, in the early stages, on the distribution, character, and evolution of the individual eruptions, above all on the evolution, rapid in chicken-pox, slow and gradual in small-pox.

In the later stages of chicken-pox—third or fourth day—considerable difficulty in diagnosis is sometimes presented, especially when the distribution of the eruption follows closely that of small-pox. The points to be noted are—the history of the illness, and the different phases of development of the component lesions of the eruption; papules, vesicles, pustules, and scabs being all intermixed. If the eruption be at all copious, lesions will be seen in all stages, papules, abortive vesicles, unruptured vesicles filled with turbid or puriform contents, flattened pocks of varying sizes with dirty, sometimes black, scabs; while the edges of the pock are often irregular and puckered, not infrequently shewing a spreading margin with the surrounding skin reddened. The irregular puckering of the periphery of the pock is very characteristic of the ruptured scabbing chicken-pox vesicles. The evolution of the eruption in small-pox is more uniform than in chicken-pox, and the combination of abortive vesicles, mature unruptured vesicles, and flattened scabbing puckered pocks, is not seen in the former disease.

It is perhaps advisable to direct attention to a point that is often overlooked in regard to the eruption of chicken-pox. It is this: on the face, forearms, hands, legs (from the knee), and feet, the vesicles of chicken-pox often bear a strong resemblance to those of modified small-pox, being small, round, hard, not transparent, and set more deeply in the epidermis than are the vesicles on the trunk. If one relied for a diagnosis solely upon the character of the eruption present on these sites, it would be impossible in many cases to say whether the disease were chicken-pox or small-pox. It is, therefore, essential that the whole of the eruption should be inspected. In all cases of chicken-pox, if seen early enough, typical vesicles will be seen on the trunk or upper parts of the extremities, or if seen later in the disease, the character of the eruption will be such as has been already described.

Cases of small-pox in unvaccinated children have frequently been mistaken for chicken-pox; but if due regard be had to the distribution of the rash, and above all to the rule that in chicken-pox some of the vesicles at least have reached their full development within one day from the appearance of the papule, while in small-pox in unvaccinated subjects the vesicles are not fully developed until five days after the appearance of the eruption, no mistake ought to be possible. Mistakes of this nature have again and again been the cause of small-pox outbreaks.

Syphilis.—Usually the scaly-papular and the pustular eruptions are mistaken for small-pox; in some cases the history of the gradual

appearance of copper-coloured scaling papules and the symmetrical distribution will at once suggest syphilis. If copper-coloured papules co-exist with scaling papules and pustules, a mistake should not be possible, but if there have been high initial fever of a few days' duration, followed by a general papular eruption becoming in part at least vesicular or pustular, the diagnosis may present some difficulty. In most if not in all such cases of syphilitic eruption there are flat, copper-coloured, scaly papules along with vesicles or pustules, and the evolution of the eruption is slower than in small-pox. Such a combination never occurs in small-pox, and many mistakes made in the diagnosis of pustular syphilides might be avoided if this point were carefully noted. If, in addition, the temperature do not fall with the appearance of the eruption, there should be no doubt whatever as to the exclusion of small-pox as a possible diagnosis; while the invariable presence of enlarged inguinal lymphatic glands, and the history of the case, add to the certainty of its being syphilis, not small-pox; here again an examination of the entire surface of the skin should not be omitted.

Herpes.—A cluster of papules arise on a circumscribed area of inflammation, become vesicular by the end of the first day, are transparent and filled with a clear fluid, and collapse on being pricked. If present on the palate and fauces they look not unlike the vesicles of small-pox, but the distribution of the rash and the absence of the initial symptoms of small-pox ought to remove any difficulty as to the diagnosis.

Eczema.—Here again the initial symptoms of small-pox are absent; the vesicles are small, and arranged usually in clusters on an inflamed base which is larger than the papule of small-pox.

Glanders.—Pyrexia, malaise, and pains in limbs are present before the skin lesion appears. The eruption is at first composed of red papules; these are indurated and increase rapidly in size till they are about as big as a pea. Pustules form on the top of the papule. There is a fetid nasal discharge. The initial symptoms and course of the eruption and of the disease are totally unlike the symptoms and course of small-pox; while the severity of the constitutional symptoms is out of all proportion to those that accompany a case of small-pox with a like amount of eruption. Moreover, nasal discharge is very rare in small-pox. If inoculated, the local wound, character of the eruption, and the history of the case, suffice to exclude the diagnosis of small-pox.

Pyæmic Skin Eruptions.—Those mistaken for small-pox usually occur in cases of infective endocarditis presenting an eruption of a small number of petechiæ and pustules. The petechiæ vary from the size of a lentil to a split pea, are irregular in outline, of a red tinged with purple colour, and distributed mostly on the extremities; interspersed with these are small pustules. The gradual onset of the symptoms, the date of the appearance of the eruption, its sparseness, the absence of deep violet or purple spots, the continued high temperature, the great prostration and severe constitutional symptoms, negative the diagnosis of small-pox.

Enteric Fever.—If the eruption be present on the trunk, limbs, and perhaps on the face, the rose-spots much raised and more or less resistant, or if some of the spots shew minute vesiculation, the disease may be mistaken for small-pox. The history, symptoms, and duration of illness, one week at least before the appearance of the rash, should remove any doubt as to the nature of the ailment.

Prickly heat may be excluded by the absence of the initial symptoms and temperature of small-pox.

In *bromide and iodide eruptions* the initial symptoms and pyrexia of small-pox are absent. The vesicles sometimes closely resemble those of small-pox in distribution, size, shape, and contents, but they do not shew depressed centres, nor a narrow white ring at the periphery. If the vesicular contents be analysed bromine or iodine will be detected. When the eruption shews as very large vesicles and bullæ there should be no difficulty in diagnosis. Inquiry should be made with regard to the nature of medicine that the patient may have been taking.

Rheumatic Eruptions.—It is only when there is an eruption of miliary vesicles markedly larger than those usually associated with rheumatism that mistakes are made. Unlike small-pox, the eruption is most abundant on the trunk. The vesicles are small, hemispherical, filled with a clear or straw-coloured fluid, and collapse on pricking. The history of rheumatism or other disease attended by sweating, the absence of initial symptoms of small-pox before the eruption appeared, its distribution and character, should exclude small-pox.

Acne.—Initial symptoms of small-pox wanting. The eruption is distributed on the face and shoulders. The pustules are acuminated, some of them indurated, and they shew a central dot or comedo.

Lichen.—The papules are soft and red, and do not become vesicular; there are no initial symptoms.

Pemphigus.—The initial symptoms of small-pox are absent; the bullæ are much larger than small-pox vesicles; they are distended by clear, straw-coloured fluid, and collapse on being pricked.

Urticaria Papulosa.—The wheals are small, of the size of a split pea, and of a dull white colour; they rise in an hour or two to the full size, either with no redness at the base or that of the usual erythema of urticaria. The vesicle is hard like the small-pox vesicle, but in urticaria it attains the size of a split pea in a few hours; the initial symptoms are not those of small-pox.

Chemical irritants sometimes produce a vesicular eruption indistinguishable from that of small-pox. I have seen a confluent vesicular eruption on the forearms and hands, with a few vesicles on the nape of the neck, mistaken for small-pox. The vesicles were of the size of those of natural small-pox on the fifth day of eruption. The limitation of a confluent vesicular eruption to the forearms and hands, and the complete absence of eruption on trunk and extremities, negatived the diagnosis of small-pox. In addition initial symptoms were absent, and the rash had attained its height within two days from the time that the patient had immersed his

arms in a strong solution of washing-soda. The vesicles on the nape of the neck were accounted for by the patient having scratched the spot with his wet fingers.

The diseases enumerated above are instances of cases of erroneous diagnosis that came under my notice during the years when all small-pox cases in London certified for removal to hospital passed through my hands for verification of the diagnosis. To avoid mistakes in the diagnosis of eruptions which counterfeit that of small-pox, be it the natural or modified small-pox, is not perhaps possible in every case; but a careful examination of the entire surface of the skin, with full inquiry as to the history of the case, will obviate the occurrence of many errors in diagnosis. The great practical importance of the diagnosis, and the anxiety with which doubtful cases are regarded, must be my excuse for the detail with which I have gone into this part of the subject.

Prognosis.—A. General considerations affecting prognosis.

These are age, vaccination, and, in a minor degree, the sex of the patients. The following table shews the fatality of small-pox in unvaccinated and vaccinated patients in the different quinquenniads up to thirty:—

TABLE of Cases, Deaths, and percentage Mortality in the Quinquennial Periods up to Thirty.[1]

	Vaccinated.			Unvaccinated.		
	Cases.	Deaths.	Mort. p.c.	Cases.	Deaths.	Mort. p.c.
Under 5 years	35	0	0	948	400	42·19
5–9 ,,	235	2	0·8	796	128	16·08
10–14 ,,	675	7	1·04	550	92	16·72
15–19 ,,	1,488	24	1·61	337	65	19·28
20–24 ,,	2,086	78	3·59	225	57	25·33
25–29 ,,	1,851	107	5·77	147	53	36·05
30 and upwards	4,627	616	13·31	220	101	45·90
Totals	10,997	834	7·6	3,223	896	24·7

It will be noted that the mortality in vaccinated subjects is almost nil under 10 years of age, very slight from 10 to 19, and thereafter increases considerably. In unvaccinated subjects the most fatal periods are under 5 and over 30 years of age, while the lowest mortality is between 5 and 14.

The character of the vaccination also affects prognosis.

[1] From Reports of Statistical Committee of Metropolitan Asylums Board. 1889 to 1904.

TABLE of Cases, Deaths, and percentage Mortality of Patients with one, two, three, and four or more good and indifferent marks.[1]

No. of Marks.	Character of Marks.	No. of Cases.	Deaths.	Mortality p.c.
One	Good	1,095	70	6·4
	Indifferent	2,044	341	16·7
Two	Good	1,461	54	3·7
	Indifferent	2,476	279	11·2
Three	Good	1,095	41	3·7
	Indifferent	1,778	133	7·4
Four or more	Good	826	23	2·7
	Indifferent	949	46	4·8
	Total	11,724	987	8·1

This table shews that while the mortality among cases with one good mark is 6·4 per cent, among those with one indifferent it is 16·7. Among those with two good marks it is 3·7; among those with two indifferent marks it is 11·2. Among those with three good marks it is 3·7 per cent, and in those with three indifferent it is 7·4. Among those with four or more good it is 2·7; among those with four or more indifferent it is 4·8. Good marks are those with a well-foveated surface, and indifferent are those shewing faint foveations or smooth surface.

If efficient vaccination be estimated by superficial area of marks the difference is even more striking. I carefully noted the area and character of the primary vaccination marks in 5808 consecutive cases of small-pox. At the time my observations were made, one-third of a square inch of well-foveated surface was held to constitute efficient vaccination. There were 1435 patients shewing efficient vaccination, of whom 36 died, giving a mortality of 2·5 per cent; and 4375 patients shewing imperfect vaccination, of whom 378 died, giving a mortality of 8·7 per cent. So that the protection against fatal attack is about three or four times greater among patients with efficient than among those with non-efficient vaccination.

Should a person who has been successfully revaccinated contract small-pox, the risk of the attack proving fatal is very small indeed, unless small-pox be superadded to some pre-existent serious disease, for example, of kidney, lung, brain, etc. There are, however, some exceptional persons in whom the protection against small-pox afforded by vaccination and revaccination, or previous attack, does not last more than a year or two; and it is impossible in all cases to promise immunity from an attack of, or even death from, small-pox after vaccination and revaccination. But I have not seen a fatal case of small-pox in any one who had one-third of a square inch or more of well-foveated primary vaccination scars and had been successfully revaccinated.

Sex does not appreciably affect prognosis, the mortality in males being only 1 per cent higher than in females.

[1] Compiled from Reports of the Medical Superintendents of the Asylums Board Small-pox Hospital from 1871 to 1886.

The nature of the prevailing epidemic affects prognosis to some extent; for instance, the epidemic of 1871 was considerably more fatal generally than the outbreaks for some time before or since.

B. Special considerations affecting prognosis.

Serious antecedent or co-existent illness affects prognosis unfavourably, and small-pox when it attacks alcoholics often assumes the vesicular or pustular hæmorrhagic form, the prognosis being then most unfavourable.

The duration of the incubation-period hardly affords reliable indications as to the severity of the subsequent attack, but some have noted that, in pure hæmorrhagic cases, it is not infrequently shorter than the average.

Considerable assistance in prognosis may be derived, however, from a consideration of the early symptoms, the appearances presented by initial rashes, the amount of the characteristic eruption, and particularly from the hæmorrhagic manifestations.

Initial Symptoms.—If these be mild the attack will probably not be fatal. But the converse does not hold good, for although in the majority of confluent and in all pure hæmorrhagic cases the initial symptoms are severe, yet severe initial symptoms often usher in a mild attack.

Initial Rashes.—General Erythemas.—General scarlatiniform and morbilliform erythemas are usually followed by mild attacks, especially in vaccinated subjects. On the other hand, a vivid red general erythema is often met with in patients whose attacks prove to be of the hæmorrhagic type. If a general erythema be accompanied by an abundant crop of purple petechiæ in the groins or elsewhere, the case will probably prove fatal; and if accompanied by isolated ink-spots death will result.

Partial Erythemas.—Partial erythemas unaccompanied by hæmorrhagic signs indicate every probability of a mild attack following. If petechio-erythematous rashes shew only the bright red petechiæ the case will probably recover. If, on the other hand, there be masses of purple petechiæ in the abdomino-crural triangle or in the lumbar region the case will most likely be fatal. If a petechial rash be composed of bright red and purple petechiæ, the case is likely to be severe; if vaccinated, the case will probably recover; if unvaccinated, it is not unlikely to end in death.

Generally speaking, the probability of a severe attack following an initial rash is directly proportioned to the depth of the purple hue or the degree of the duskiness of the rash. Blood in the urine in the initial stage is an unfavourable symptom, as is also hæmorrhage from mucous surfaces and the uterus.

In discrete modified small-pox the prognosis is very good; death rarely occurs. In discrete natural small-pox prognosis is unfavourable under one year; less so between one and three years of age; after that good. Convulsions and coma in modified or unmodified discrete small-pox are unfavourable, especially so if they supervene from about the sixth to the ninth day of disease.

Confluent Modified Small pox.—When vaccinated adults shew a copious,

almost confluent eruption, it is, during the first few days, impossible to say whether or not the disease will be modified. If, on the third or fourth day of eruption, the vesicles on the face, which is usually at that date markedly œdematous in these cases, begin to get cloudy it may then be safely affirmed that the attack will be modified, and that the patient will, in all probability, recover.

Confluent Unmodified Small-pox.—Gravity of prognosis bears a direct ratio to the degree of confluence of eruption. If quite confluent on the face, head, extremities, and back, the prospect of recovery is slight; but if the eruption be not confluent on the back the chance of recovery is much greater. Abortion affects prognosis very unfavourably. Under two years of age confluent natural small-pox is almost invariably fatal; from two to five years about one-fourth of the cases recover; the prognosis thereafter is more favourable, and from ten to fourteen the patient is more likely to recover than at any other age. After fifteen years of age the percentage of deaths to recoveries increases steadily with advancing years.

In all cases, abundant eruption on the mouth, fauces, and pharynx is unfavourable; and if symptoms of laryngeal obstruction supervene, the gravity of the prognosis is increased. Subcutaneous œdema is not in itself unfavourable; on the other hand, if the vesicles fill with lymph very slowly, and the skin at the fifth or sixth day of eruption presents a flat, pasty white, or rough parchment appearance, accompanied by very little swelling (other than that caused by the raised epidermis), the prognosis is most unfavourable, recovery rarely taking place, and then, as a rule, only in patients between ten and twenty years of age.

Delirium in the vesicular stage, and, in children, grinding of the teeth are unfavourable. If the temperature in the vesicular stage do not fall under 100° F. the prognosis is less favourable than if it fall to normal. A temperature over 104° in the pustular stage, attended by restlessness and delirium, is unfavourable; and if septicæmia, deep cellulitis, laryngeal or pulmonary complications, or diarrhœa follow, the gravity of the prognosis is increased.

Hæmorrhagic Small-pox.—True hæmorrhagic small-pox is invariably fatal. Where hæmorrhagic manifestations and the eruption of small-pox co-exist, prognosis becomes less grave as the attack more nearly assumes the form in which the skin hæmorrhages are limited to sub- and peri-vesicular hæmorrhages; but in all such cases the prognosis is exceedingly unfavourable, and recovery very rarely takes place. In sub- and peri-vesicular hæmorrhagic cases, if the eruption be discrete and hæmorrhage appear late and be limited mostly to the lower extremities, recovery is to be hoped for; but if the eruption be abundant, and sub- and peri-vesicular hæmorrhage general, recovery is very doubtful. If the eruption be confluent with general sub- and peri-vesicular hæmorrhage, recovery does not take place; but a considerable number of confluent cases recover if hæmorrhage be present only in the lower extremities, and to a limited extent on the trunk and arms. The presence of a claret-coloured areola

encircling the majority of the vesicles early in the course of eruption is a most unfavourable sign. It often appears on the second day of eruption, and affords early evidence as to the probable termination of the disease. If it be confined to the lower extremities, it is not in many cases of much significance. In all forms of hæmorrhagic small-pox copious hæmorrhage from the mucous membranes deepens the gravity of the prognosis.

The onset of serious lung complication during the pustular and incrustation stages is unfavourable, as are also extensive erysipelas of the extremities and deep cellulitis.

Nursing and Management of Patients.—Careful and judicious nursing and the most scrupulous attention to the cleanliness of the bed-linen, are all-important. The pus oozing from the pustules very quickly soils the personal and bed linen, which should therefore be changed very frequently. The mouth and nose should be frequently cleansed, and above all in severe attacks the eyes should be watched constantly, and be bathed and cleansed systematically and thoroughly. It is impossible to overrate the importance of this attention.

The handling of the patients must be most gentle, and in raising the head or shoulders the nurse's arm should always be placed under the pillow. Infants, when being nursed in the arms, should rest on a pillow on the nurse's arm. Attention to details of this kind add much to the patient's comfort.

In the acute stage it is not practicable to wash patients suffering from severe or even moderately severe small-pox; but the skin should be cleansed as much as possible by sponging, and such ablutions as will readily suggest themselves to an intelligent nurse carried out; baths should be given as soon as the patient can bear the fatigue.

The management of delirious patients requires much tact and intelligence on the part of the nurse. The most troublesome and violent delirium is noted usually in confluent cases during the late vesicular stage or at the beginning of the pustular. These patients require most careful and constant watching. Very often they seize the occasion of the nurse's temporary absence to make their escape through door or window. For this reason they should not be left unattended for an instant. Most commonly the patient has the strongest objection to being considered ill, wishes to go home, and insists upon having his clothes given him. A judicious nurse will endeavour to distract his attention, talk to him, humour him as much as possible, tell stories, prevaricate, do anything but argue with or contradict him; and must never, except in some extremity, use mechanical restraint, and then only as a purely temporary measure. Mechanical restraint is most inadvisable, aggravating the patient and increasing the delirium. A delirious small-pox patient, when thoroughly roused and angry, will not hesitate to knock the nurse down and make his escape. In the case of a patient who insists that he is quite well and demands to be dressed and allowed to go home, if opiates fail to quiet him—a useful device is to dress the patient in a dressing-gown, stockings, and slippers, and allow him to walk up and down the

ward or round the room, the nurse holding the patient's arm, at the same time keeping her eye on the door and window. After a few turns, the patient finds that he is unable to continue the exercise, and goes quietly back to bed. In such cases it is necessary to have the assistance of an additional nurse or male attendant to sit by the patient's bed. If the bedroom be on the first floor or above, stops should be fixed in the sash grooves, so that neither sash can be opened wider than six inches.

Treatment.—Patients with discrete modified small-pox require little attention, but in those suffering from the severer forms, unremitting care and good nursing are essential. There should be an ample supply of fresh, cool air. The temperature of the room should be about 60° F. The patient ought not to be exposed to draughts. The air in the room should be changed at least four times every hour, and there should be no curtains or hangings to impede its free circulation. The bed- and body-linen should be of fine soft material, and the coverings light. A hair-mattress on wire makes the most comfortable bed. No matter how fine the linen, the pressure of the bed-clothes and the mattress make the patient feel as if he were sleeping on thorns. In confluent cases considerable relief is afforded by a water-bed, but air- and water-cushions are of little use.

Nourishment, Stimulants, and Diet.—Throughout the acute stages of the illness milk, mixed if necessary with diluents, is the main and most suitable article of nourishment. Water should be given liberally, and a cup of tea or coffee whenever the patient wishes. In the initial stage many patients take little nourishment, nor is it often necessary that they should take more than a couple of pints of milk daily. For the majority of patients suffering from modified small-pox, the above dietary will be sufficient during the short illness they experience. As soon as the appetite returns the ordinary diet of health should be resumed.

In the severer forms of small-pox, however, more liberal nourishment is necessary, and in many cases it is of great importance that it be given every two hours day and night. During the vesicular stage, three pints of milk with, say, a pint of mutton, veal, or chicken-broth, or beef-tea, and in addition plenty of water, is usually a sufficient daily allowance. During the pustular and incrustation stages, the strain of the disease taxes the patient's strength. This period is roughly the second week of the illness. To combat the exhaustion and prostration of this period, three or four pints of milk, two or three eggs, the raw juice of four to eight ounces of lean meat, and abundance of water should be given. The eggs are perhaps best given in the form of egg-flip with or without a little brandy. The raw meat juice should be given mixed in milk.

Should the pulse become weak, alcoholic stimulants should be given in quantity proportional to the degree of prostration and cardiac weakness. Patients will often be benefited by brandy or whisky given freely, and the stimulant should not be discontinued till the condition of the patient permit, and then gradually. Champagne is a useful stimulant in

pronounced prostration and exhaustion. Vesicular hæmorrhagic cases sometimes shew marked prostration during the vesicular stage and may then require alcoholic stimulants with eggs, and so forth. In pure hæmorrhagic cases it is sometimes desirable to give alcohol to lessen the patient's distress, but although it may alleviate suffering and perhaps prolong life a little, it will not avert a fatal issue.

When there is continued vomiting the milk should be peptonised or mixed with diluents such as barley- or lime-water. Should the vomiting persist recourse should be had to rectal feeding. In the feeding of babies and infants, care should be taken not to overload the stomach with too much milk, as this is a common cause of vomiting.

Pieces of ice allowed to melt in the patient's mouth are most cooling and agreeable in all severe cases, especially when there is much buccal and faucial eruption and swelling. Lemonade made with fresh lemons helps to quench the thirst. In the rare instances in which patients are unable to swallow or refuse to take nourishment by the mouth, feeding by the nasal or stomach-tube should be tried, but it may be difficult to pass either of these, and rectal feeding may have to be adopted.

In the more severe cases, as soon as the appetite begins to return the patient should be given light and digestible solid food, milk puddings, custard, boiled fish, chicken, and so on, at first; when the appetite improves the ordinary diet of health should be resumed. The appetite during convalescence is often ravenous, and should be gratified as far as practicable and advisable.

During convalescence from severe small-pox, when the appetite is sluggish and the patient is regaining strength slowly, wine is very beneficial, port being perhaps the most suitable. To many convalescents malt liquors may be given with advantage.

In confluent attacks, during the vesicular and pustular stages, deglutition may be difficult and painful. Small pieces of ice placed in the patient's mouth will often afford considerable relief. The patients usually keep the mouth open, consequently the mouth and throat, covered with disintegrating vesicles and secretion, become dry, and as a result deglutition is difficult. This can in the main be obviated by carefully cleaning the mouth and fauces frequently, and is most satisfactorily accomplished by using swabs moistened with a solution of boric acid or other suitable wash. After swabbing, the mouth and throat should be brushed with glycerin of borax or a solution of boric acid in glycerin. If the patient be capable of rinsing the mouth himself, a good wash for the purpose is one of liquor potassæ 3 drms., and acid carbol. 1½ drms., to a pint of water. The fetid breath, which often marks these cases, will be much lessened by these measures. For painful deglutition painting the fauces with a weak solution of cocaine before the feeds has been recommended; in about five or ten minutes the patient will be able to swallow comfortably.

Local applications to the skin are useful in order to allay the excessive irritation, to remove the pus oozing from the pustules, to lessen the smell,

to accelerate the separation of the crusts, to prevent in some measure septic absorption, and to hasten the healing of the ulceration, thereby diminishing pitting and disfigurement. The itching and irritation are often best relieved by cold moist applications, such as boric lint, very frequently moistened and renewed as required. I have used oils and vaseline, but have generally found that they increased the irritation and sensation of heat, especially during the vesicular and earlier pustular stages. Antiseptic dusting powders, such as creolin, boracic, winter-green, and the like, are undoubtedly useful in allaying smell, but they have the disadvantage of favouring the formation and adhesion of crusts under which ulceration of the skin can proceed unchecked. A cold-cream with four parts of salicylate of soda to one hundred of cream has been found to allay the smell in the suppurative stages (Dujardin-Beaumetz). Undiluted tincture of iodine has been employed by Welch and Schamberg as a local application. It is painted on the face as early in the disease as possible, once or twice daily, and may be diluted to one-half the strength if the skin be very sensitive. About the eighth to the tenth day a parchment-like mask is formed, which begins to crack and peel off. They believe that the application of iodine tends to make the pustules shrink, to hasten decrustation, and that to some extent it lessens pitting, and that the liability to subsequent pyogenetic complications of the skin appears to be diminished.

When the eruption is quite confluent, and the patient tears the epidermis off extensive areas, it is necessary to muffle the hands, while the oozing cutis should be covered by some suitable cold, moist, antiseptic dressing. In all cases in which the eruption is copious on the scalp the hair should be cropped short early in the disease.

The early separation of the crusts on the face and scalp is most desirable. This can best be accomplished by the application of linseed-meal poultices. On the scalp a fairly thick poultice, with iodoform on its surface, may be applied in the ordinary manner; on the face the method most agreeable to the patient is as follows: Cut a mask of a single thickness of lint, with apertures for the eyes, nose, and mouth; smear a thin layer of linseed poultice on this, taking care to put on the surface a little vaseline in which iodoform has been mixed (greasy applications do not at this stage irritate the patient), and apply it to the face, changing it every two hours at least. The crusts may be removed more rapidly by this means than by any other. It is important that the crusts should be separated from the face as soon as possible, in order that suitable antiseptic dressings may be applied to the ulcerating surfaces. To the arms, legs, and other parts, boric, weak formalin, or other moist antiseptic dressing should be applied. The importance of these moist applications in the incrustation and decrustation stages cannot be over-estimated. Tepid or warm baths one-half to one hour in duration may be given daily, with the view of facilitating the separation of the crusts and cleansing the skin of the trunk and limbs.

During convalescence from severe small-pox the skin is often very

tender and rough; consequently the friction of the clothing causes much irritation of the skin and discomfort. Much relief is obtained by rubbing the skin after the usual bath with a powder, such as pulv. zinci oxid.; pulv. amyli; pulv. acid. boric; two parts of starch and one of the other two ingredients.

The ragged verrucose condition of the skin on the nose occurring in some cases may be lessened by paring off the ragged warty excrescences.

Multiple superficial abscesses should be opened as soon as they arise; those on the scalp by crucial incisions: iodoform poultices or warm antiseptic dressings are then to be applied. Deep-seated abscesses should be opened as soon as the presence of pus is detected Cellulitis, if extensive, must be incised freely, deeply, and early, and antiseptic fomentations applied.

For laryngitis a steam-tent with warm inhalations should be used. If dyspnœa be great, or œdema of the glottis occur, tracheotomy or intubation should be performed. The great swelling of the neck in small-pox renders the performance of tracheotomy somewhat difficult, and much hæmorrhage may take place.

Glossitis, if slight, subsides without interference, but the tongue may be painted with glycerin of tannic acid, and application of ice is grateful; but if the swelling be very great, it is necessary to make a free incision about half an inch deep and about two-thirds of an inch externally to the raphe.

If erysipelas occur, the affected part should be enveloped in cotton-wool, or painted with a paste made of milk and a little liq. plumb. subacetatis, and antistreptococcic serum may be injected.

With the view of checking the pustulation of the vesicles, various drugs, such as xylol, thymol, eucalyptus, sulpho-carbolate of soda, hyposulphite of soda, perchloride of mercury, have been given internally. I have not found that any arrest of pustulation followed the use of such remedies; not only did they appear to be useless, but in many instances they had the disadvantage of weakening the digestion and inducing vomiting.

Opening the vesicles with or without cauterisation has been resorted to for the purpose of preventing pitting, but the method is painful, and most authorities agree that no appreciable benefit results.

With the view of arresting the progress of vesicular growth and pustulation, vaccination has been recommended after the appearance of the characteristic eruption. It does not affect the progress of the eruption in the slightest degree.

Eyes.—It is most important in all cases in which the eyes are affected, even if only in a slight degree, that vaseline should be applied to the edges of the lids frequently, to prevent them from sticking together; otherwise discharge is pent up, and much injury to the eye may follow.

Conjunctivitis and mild ophthalmia usually yield to systematic and regular irrigation with boric solution. Should the ophthalmia be attended with very copious purulent discharge and much swelling of the con-

junctiva, solid stick of nitrate of silver should be applied daily till the condition begins to subside. When there is very great chemosis of the conjunctiva, Welch and Schamberg recommend that it be snipped, and if extreme chemosis of the lids cause undue pressure on the eye, that the outer canthus be cut.

When keratitis occurs in the course of an attack of ophthalmia, the pupil should be widely dilated by atropine, and warm boric lotion used to irrigate the eye. Should there be much increase of intra-ocular tension a paracentesis should be performed, and be repeated if necessary. In cases of keratitis, without any conjunctival injection or discharge, in which the whole cornea threatens rapidly to become opaque, the pupil must be fully dilated with atropine twice daily, and warm fomentations, made with liquid extract of opium or poppy heads in water, applied to the eye every five minutes, and intermitted for one quarter in every hour, till moderate inflammatory reaction of the conjunctiva is set up. It is essential that some of the warm fomentation should be dropped into the eye each time it is fomented. After some inflammatory action of the conjunctiva is established, the warm fomentations should be continued every hour or two hours, the eye to be kept clear of any discharge that may appear, and later recourse may be had to irrigation with warm boric lotion. Many cases of this nature do badly, the whole cornea sloughing and the eye becoming disorganised; only a few respond to treatment, which must be commenced as soon as the faintest dulling of the corneal lustre is noticed, if success is to be hoped for.

Small ulcers of the cornea yield to treatment with an ointment composed of hydrarg. ox. flav. 2 grns., atropine 4 grns., vaseline 2 drms., applied to the eye twice a day. For corneal ulcer coming on during the course of an ophthalmia, Welch and Schamberg recommend, if the ulceration be central, that atropine be dropped in twice or thrice daily. But if the ulceration be marginal a weak solution of eserine salicylate, one-quarter grain to an ounce, may be used, but with great caution, as this drug is liable to increase the hyperæmia of the iris, with consequent iritis. When the pupil is contracted the use of the drug should be discontinued. When perforation of the cornea is threatened they recommend that the edges of the ulcer be cauterised with a hot probe. During the whole course of treatment the eye must be thoroughly flushed with warm boric solutions every hour, or more often if necessary.

The drug treatment of small-pox is restricted to treating symptoms as they arise, since no drug has yet been discovered that will influence the development, or arrest the pustulation, of the eruption. With the object of mitigating the headache of the initial stage, antipyrin or phenacetin may be given, and some hypnotic, such as trional or opium, to induce sleep. Should vomiting be troublesome at this time morphine will usually allay it. A mild saline mixture may be given during the earlier period, followed by quinine, in two- or four-grain doses every six hours, when the eruption becomes fully vesicular. Should the pulse become rapid and weak, or irregular, during pustulation or later, cardiac stimulants,

such as strychnine, digitalis, and adrenalin chloride, may prove beneficial For bronchitis expectorants are sometimes useful. During recovery from severe attacks attended with emaciation, Easton's syrup, iron, quinine, and in some cases cod-liver oil, are distinctly beneficial.

During the late vesicular and the pustular stages restlessness and sleeplessness are often marked. To render the patient fairly comfortable and to induce sleep, drugs are required. In my experience tincture of opium or morphine are the best; not only do they bring rest and sleep, but a degree of comfort otherwise unobtainable.

In quieting the violent delirium of small-pox, opiates are indispensable, and large doses are frequently necessary, such as thirty drops of laudanum or half a grain of morphine, repeated in an hour or two if the delirium continues, and thereafter as required. These may be given by the mouth or hypodermically; in the more violent cases I found hypodermic injection the most suitable. In many patients it is possible to keep the delirium under control by these measures, but in some hæmorrhagic vesicular and pustular cases it is impossible to control it completely. When opiates are considered inadvisable, trional or other hypnotic may be given. In some cases I have found that two or three ounces of brandy in hot water, given as a draught in the evening, will enable the patient to rest and sleep comfortably during the night. While many patients object to ordinary sleeping draughts, they generally take brandy readily.

For the reduction of high pyrexia during the pustular stage antipyresis may, in some cases, be deemed advisable. If the temperature be high and long continued, antipyrin or phenacetin in 10- or 15-grain doses will in many cases temporarily reduce the pyrexia. Where circumstances permit a tepid bath 90° to 95° F., given and repeated as required, is useful, and will moderate the pyrexia and add to the patient's comfort. Continuous tepid baths are recommended by some, who assert that by their use not only is the pyrexia reduced, but the early maceration of the pustules is effected, the formation of crusts and scabs prevented, and the septic absorption through the skin very much lessened. Cold baths are not often administered, but if it be considered advisable to do so the temperature of the bath for adults should be 80° to 75° F., reduced while the patient is in the bath to about 70°, and for children 85° F., reduced to about, but not below, 75°. The duration of the immersion should be from ten to twenty minutes, as the condition of the patient may indicate. In most cases it is necessary to give a little brandy before the patient is bathed.

In black small-pox attended with hæmorrhage from the mucous surfaces I have administered ergotin, hazeline, and other hæmostatics with the view of checking it, but little or no benefit has resulted.

Constipation should be relieved by agreeable but effective aperients, aided, if necessary, by suitable enemas. Diarrhœa, which usually occurs only in severe cases, may often be checked by such astringents as chalk and catechu, combined, if necessary, with opium.

Red light treatment, in which the actinic or chemical rays are

excluded, has been advocated and used by Finsen and others for the prevention of suppuration of the vesicles. The success claimed for this method has not been confirmed by the most recent observers. Dr. T. F. Ricketts tried it in cases carefully selected, partly as being in a very early stage of the disease, and partly as being likely to develop suppuration in the lesions. He states that in no instance did the development of the eruption and the progress of the cases differ from what would have been expected had the patients been treated in the ordinary way.

Serum-therapy.—Vaccinal serum, obtained from immunised heifers, has been used by Béclère, Thomson and Brownlee, and others in the treatment of small-pox with the view of arresting the pustulation of the vesicles. The dose required is very large, equivalent to one-fiftieth part of the body weight in adults, and to the twentieth part in children. Thus a woman weighing 70 kilograms (155 lbs.) received over 1500 c.c. ($52\frac{3}{4}$ oz.) beneath the skin in one hour. The cases treated have been too few to afford any reliable indication as to the value of this treatment. Roger states that the method is harmless, and the injection of the serum, even in large amounts, is borne perfectly (*vide* p. 756).

We may, however, hope that when a highly potent vaccinal serum is available it will be possible, by its use, to arrest the evolution of the lesion of natural small-pox, and induce an abortive pustulation in the vesicles similar to that seen in the vesicular eruption of many vaccinated small-pox patients about the third or fourth day of eruption. When this is achieved, natural small-pox will be robbed of its terrors.

The prevention of small-pox is most efficiently ensured by vaccination and revaccination, and the prompt isolation of the sick. Should small-pox break out in a family all "contacts" should be revaccinated at once. If revaccination be performed within three days of reception of infection, and if it be successful, none of those exposed to infection will develop small-pox; if done later it may or may not modify the attack should small-pox develop.

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TYPHUS FEVER

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Synonyms.—*Spotted Fever*, *Maculated* or *Petechial Typhus*; Germ. *Fleckfieber*, *Flecktyphus*, *Exanthematischer Typhus*; French, *Typhus exanthématique*; Ital. *Dermo-tifo*, *Typho esantematico*; Spanish, *Tifus*, "*El Tabardillo*" or "*Tabardiglio*" (from *tabardo*, a cloak of dark cloth worn by the peasantry in Spain); Dutch, *Vlekkoorts*, *Kwaadardigekoorts* (*i.e.* malignant fever); Swedish, *Fläcktyfus*; Norwegian or Danish, *Nervefeber*, *Exantematisk Tyfus.*

Typhus Fever is an acute, specific, highly infectious disease which prevails in epidemics; particularly in times of destitution and in the presence of overcrowding with deficient ventilation. It is characterised by a sudden onset with marked nervous symptoms, namely, rheumatoid pains, rigors, and headache. A peculiar measly or rubeoloid rash appears most commonly on the fifth day of the disease. This consists of slightly elevated spots of varying size and shape, at first deleble on pressure (*maculæ*), afterwards persistent and darker (*petechiæ*). This rash is commonly present, except in young children; but its presence must not

be considered essential to the diagnosis of typhus. It results rather from dissolution of the blood or from bacterial thrombosis than from dermatitis. There is early and usually extreme prostration both of the nervous system (*ataxia*) and of the muscular system (*adynamia*).

In the second week of the fever delirium is commonly present, sometimes of an acute and noisy type (delirium ferox), accompanied, it may be, by much muscular agitation and restlessness (delirium tremens), but oftener of a low, listless, muttering kind with somnolence (typhomania of Galen). In this case there is a tendency to stupor or coma.

The fever terminates by a crisis, which generally happens on or about the fourteenth day, and takes the form of a deep and prolonged sleep, a diuresis with deposits of urates in the urine, a moderate diarrhœa, or slight diaphoresis with quickly reviving intelligence. Profuse clammy sweating at the time of crisis is universally and justly regarded as a most unfavourable sign. Its occurrence is associated with extreme nervous prostration; a condition which constitutes the so-called "typhoid" or "ataxic" state.

During the fever the mucous membranes are generally the seat of a passive catarrh; and as the bronchial tract is the most affected, the disease used to be called "*catarrhal typhus*" in Ireland, while Rokitansky named it "*bronchotyphus*" or "*pneumotyphus.*"

In fatal cases no specific lesion is found beyond a widespread congestion and "dissolution of the blood," as well as a granular degeneration and cloudy swelling of the nerves, muscles, and great viscera. None of these lesions, however, is of constant occurrence or peculiar to typhus.

The Greek term τῦφος (*smoke*, *mist*, *fog*) was employed by Hippocrates to define a confused state of the intellect, with a tendency to stupor (*stupor attonitus*); and in this sense it is aptly applied to typhus fever with its slow cerebration and drowsy stupor. Boissier de Sauvages first (in 1760) called this fever "typhus," and the name was adopted by Cullen of Edinburgh in 1769. Previous to the time of de Sauvages typhus was known as "Pestilential" or "Putrid Fever," or by some name suggested by the eruption, or expressive of the locality in which it appeared, as "Camp," "Jail," "Hospital," or "Ship Fever" (Murchison).

Etiology.—Typhus is mostly a disease of the temperate and cold zones, a result which is in great measure due to the mode of living adopted by people resident in cold climates. They congregate in badly ventilated houses rather than live an open-air life. This fever has from time to time prevailed in all parts of Europe, but it has had its peculiar habitats in Great Britain and Ireland, and in Russia. In the United States and British North America it has prevailed epidemically at various times since 1807, when it made its first appearance in the New England States. In Philadelphia it broke out in 1812, continuing to shew itself sporadically until 1836 (H. Amory Hare). It is hardly known in Australia, New Zealand, India, Africa, or in the tropical and subtropical parts of North and South America. The Irish race has been especially prone to the disease, probably from the habits and comparative poverty

of that people. "The history of typhus," Hirsch observed, "is written in those dark pages of the world's story which tell of the grievous visitations of mankind by war, famine, and misery of every kind." He added, "The idea that overcrowding in filthy and unventilated rooms affords the essential condition for the development of typhus-foci and for the spread of the disease has been completely borne out by the experience of all times." Epidemics of typhus are yearly becoming more and more rare. The most recently recorded British outbreak is one which occurred in Sheffield in 1890, and was described by Dr. Theodore Thomson, Inspector of the Local Government Board (England).

In practically all cases typhus arises from the reception into the system of a specific poison. Of the intimate nature of this poison we are still ignorant, although analogy points to some micro-organism or its products as the *causa causans* of the disease. Hlava (1891) and Lewaschew (1892) are among the most recent writers on the bacteriology of typhus. In 1894, Kelsch suggested the hypothesis that the cause of typhus is a micro-organism which is usually innocuous, but becomes pathogenetic under special conditions of environment. Nothing definite, however, has as yet resulted from their researches or those of other investigators.

The *materies morbi* is cast off in the breath, from the skin, possibly in the evacuations also. It is then conveyed through close air, or by fomites, and, inhaled or swallowed, finds its way into the blood of fresh victims. There is no evidence that the poison of typhus is transmitted through liquid media. It is certainly not carried by water, nor does it bear any relation to the soil. Actual contact with the sick is not essential for the transmission of typhus; yet the striking-distance of this fever is not great. Unlike the contagia of small-pox and scarlatina, the poison of typhus does not cross open-air spaces; it is readily neutralised, probably by oxidation, on coming into contact with fresh air. It is quickly absorbed by articles of clothing, bedding, furniture, and beams of wood; particularly by dark-coloured rather than by light-coloured woollen articles of dress. Such carriers of infection are technically called "fomites" (Lat. *fomes*, *fomitis*, touch-wood, tinder). Typhus is non-inoculable, but eminently infectious or "catching." There is no evidence that it is communicable to the lower animals. One attack generally confers immunity from a second. The disease is infectious or "catching" in all its stages, probably most so during the period of defervescence and in early convalescence—that is, when the patients are desquamating. Answering the question, "At what period of the disease is the danger of infection greatest?" Curschmann says, "Undoubtedly at the beginning and at the height of the febrile stage." He regards infection as possible during the period of incubation, and as absolutely certain during the initial stage (invasion). In support of the former of these two statements, he recalls an instructive case which he saw when a student. One of his fellow-students became infected as the result of spending an hour in a typhus fever patient's room, at a time when the patient had as yet no fever, and complained only of slight general malaise, depression, and pain in the head and back.

Even the bodies of those dead of typhus may, under certain conditions, transmit the disease. Its poison is very volatile and lighter than atmospheric air. There is strong presumptive evidence that dry heat (96° C. = 204·8° F.) is a powerful disinfectant agent in the preventive treatment.

Curschmann considers it is probable that the contagium continues to reproduce itself in the immediate surroundings of the patient for some time before and after, as well as during, the febrile period. He thinks that this contagium undoubtedly attaches itself to the dust in the atmosphere, and is very easily transferred to inanimate articles handled by, or close to, the patient, such as clothing, underwear, bedclothes, curtains, carpets, upholstered furniture, and in fact, all objects with a rough woolly surface. If such objects are protected against contact with air, particularly air in motion, the contagium clinging to them may maintain its vitality for many months, and the disease may thus be carried to distant localities, where it was not prevalent at the time, and where it is not endemic. For example, in Hamburg a furrier was attacked by typhus ten days after he had received a consignment of furs from an infected district in Poland. He had not been absent from home for months, and had not come into contact with any one suffering from the disease, while more than a year had elapsed since the last sporadic case of typhus fever had occurred in Hamburg. The disease was traced to the infected articles before they had been put on the market. They were immediately disinfected, and there was no further spread of the disease.

The doctrine of the *de novo* or spontaneous generation of typhus is opposed to all analogy, so far as the specific fevers are concerned; indeed it is beset with greater difficulties than those which it is designed to explain. Further, it is unnecessary if we assume the microbic origin of this fever, and remember how great is the vitality of the contagium, if only it is prevented from coming into contact with fresh air. It must, however, be admitted that now and again a case of typhus occurs in which it is impossible to trace the infection. A striking example is reported by Surgeon-General R. H. Quill, R.A.M.C.

The *bacteriology* of typhus fever is still imperfect. Researches on the subject have been in progress since 1868, when E. Hallier, of Jena, announced his discovery of a typhus fungus (*Rhizoporus*). In 1883 Dr. Mott described actively motile dumb-bell cocci in the blood of typhus. In 1891 Hlava of Prague found in the blood in twenty out of thirty-three fatal cases of typhus a peculiar, well-defined bacterium, to which he gave the name of *Streptobacillus*, and which he regards as the cause of the fever. Lewaschew, in 1892, described organisms which he had found in the blood of the spleen or finger of typhus patients, and which he regarded as a cause of the disease. In fresh blood these organisms appear as small, round, highly-refractive, actively moving bodies, lying between the corpuscles. Sometimes the organism is oval in shape and flagellate, or it may appear as a thread slightly enlarged at one end. These are probably different forms of the same microbe. Lastly, Dubieff and

Bruhl (1893) found in the blood and spleen a diplococcus, called by them *Diplococcus exanthematicus.*

An individual is rendered more susceptible to the influence of the primary exciting cause of typhus by certain accidental circumstances, themselves insufficient to generate the fever, to which the term "predisposing causes" is applied. The chief predisposing causes of typhus are, in the order of their etiological importance, destitution and defective nutrition, overcrowding, bad ventilation. In addition to these, the prevalence of typhus is more or less favoured by the winter season, intemperance, recent residence in an infected locality, previous illnesses, bodily fatigue and pain, loss of sleep, mental anxiety, and depressing emotion such as sorrow, fear, disappointment, and worry. In the presence of a group of these factors a small and hitherto inert dose of the fever-poison may kindle a serious attack of typhus in such a way as to suggest that the fever has arisen spontaneously or *de novo.*

Morbid Anatomy.—Cadaveric rigidity is of short duration, and putrefaction takes place rapidly. Emaciation is sometimes considerable, though much less than in enteric fever, owing to the shorter course of typhus and to the absence of intestinal lesions. Widespread congestion (passive hyperæmia) is the most constant and noticeable post-mortem appearance. The petechiæ persist after death, and the blood in general is profoundly altered, being feebly coagulable, often staining the endocardium and the intima vasorum. Examined under the microscope rouleaux are absent, and the red blood-corpuscles are crenated and misshapen. Oligocythæmia and leucocytosis are usually observed—the latter condition affording a diagnostic from enteric fever (Combemale). The muscular tissue of the heart is softened and friable. It is the seat of cloudy swelling and granular fatty degeneration. In the respiratory system there are traces of a widespread catarrhal inflammation of the air-passages and of hypostatic consolidations in the lungs. Curschmann has seen five cases of pulmonary gangrene in typhus, all due to aspiration of putrid matters in perichondritis of the larynx. No evidence of acute inflammation of the brain or its membranes is forthcoming as a rule to account for the cerebral symptoms. The kidneys are not uncommonly hyperæmic and enlarged, while the tubes are stuffed with granular epithelium. Notwithstanding the more or less frequent occurrence of the foregoing pathological changes, we may conclude with Murchison that "there is no obvious lesion constant in or peculiar to typhus."

Clinical Description.—In typhus fever there seems to be no fixed duration for the *period of incubation* or the *latent stage.* In a large number of cases it is about twelve days; it rarely, if ever, exceeds three weeks. In many instances (one-third or more) it is less than twelve days, and occasionally there is scarcely any latent period, the symptoms commencing almost at the instant of exposure to the poison. Frequently the patients are conscious of the moment at which the fever-poison enters the system. One or two days of slight indisposition, shewn by lassitude,

vertigo, slight headache, and loss of appetite, may precede the actual onset of typhus, which is sudden. The earliest symptoms are referable to the nervous system; they are chilliness or slight rigors, languor, frontal headache, pains in the back and limbs, especially the thighs. Giddiness, noises in the ears (*tinnitus aurium*), and disturbed sleep or sleeplessness are commonly present. If sleep occur it is haunted by dreams, and the patient rambles in his sleep. A sense of complete exhaustion quickly overwhelms the sufferer, so that by the third day he is fain to take to his bed. In this, the *stage of invasion*, other symptoms are loss of appetite, constipation, sometimes nausea without vomiting, coated tongue, quick pulse, flushed and dusky face. The expression at first betokens weariness, but soon becomes dull, heavy, and listless. Afterwards the aspect becomes vacant and bewildered, sometimes wild and defiant. The face is flushed, with a dusky, earthy, or leaden hue. Such is the *facies typhosa.*

The *stage of nervous excitement*—also called the *eruptive stage*—follows. It commonly extends from the appearance of the rash on the fourth or fifth day until the commencement of somnolence or stupor. Its leading features are restlessness, wakefulness, and delirium. During this stage headache gives place to raving, and the tongue grows dry and brown; sordes collect on the lips, teeth, and gums, and, becoming black from desiccation, have a heavy, offensive smell. The presence of abundant deposits of sordes is so far a proof of a severe attack and of seriously impaired vital powers.

The rash, or exanthem, of typhus in its earlier stage often closely resembles that of measles; hence the terms "morbilliform," "rubeoloid," and "measly" are often applied to it. It consists of spots or maculæ of very irregular size and outline, and of a dirty pink or florid colour. These appear first near the armpits and on the wrists, then on the sides of the abdomen, afterwards on the chest, back, shoulders, thighs, and arms. They are rarely seen on the face and neck. At first, and particularly in mild cases, these maculæ are slightly elevated and deleble on pressure, like the velvety papules of measles. They have, however, no defined margin, but merge insensibly into the colour of the surrounding skin. Beneath the cuticle another crop of maculæ often appears, causing a characteristic marbling or mottling of the skin, hence the expression "subcuticular mottling." The superficial spots and the deeper mottling together constitute an eruption, to which Sir William Jenner gave the name of the "mulberry rash" of typhus.

Towards the *close of the first week* headache commonly gives place to delirium or raving, which may last up to the time of the crisis. The delirium is sometimes acute and noisy like mania (*delirium ferox*); sometimes more like that of excessive alcoholism, being accompanied by muscular agitation, trembling, and talkativeness (*delirium tremens*); and sometimes of a low muttering kind (the *typhomania* of Galen). The nervous excitement is most marked towards evening and at night. Prostration takes its place in the morning.

About the tenth day the *stage of nervous prostration* succeeds that

of nervous excitement. It is also called the "putrid," "malignant," or "typhoid" ("ataxic") stage, or the "later eruptive stage." This is a most critical period in typhus, and when its ominous symptoms are well marked the patient's life hangs trembling in the balance. Extreme nervous prostration (ataxia), muscular and cardiac weakness (adynamia), defective cerebration, low muttering delirium, stupor and unconsciousness deepening into coma, are the phenomena which shew themselves in "ataxo-adynamic typhus," as this grave form of the fever is called. The patient lies on his back and sinks down in the bed (prostrate dorsal decubitus), he moans and mumbles to himself incoherently, is indifferent to all that goes on around him, looks stupid and unconscious, with injected ferret-like eyes, contracted pupils (the "pinhole pupil" of Graves), teeth coated with sordes, and dry, brown-crusted, shrivelled tongue—the "parrot-tongue" of typhus. Deafness is also a common symptom. Various involuntary movements take place, such as tremors, twitchings of the muscles (*subsultus tendinum*), spasmodic twitchings of the face, perhaps choreic convulsions, or more usually picking at or fumbling with the bed-clothes—the so-called "floccitatio" or "carphology." Obstinate hiccough (*singultus*) often accompanies these movements, and is a very grave sign. Not uncommonly, also, involuntary evacuations take place from paresis of the sphincters of the rectum and bladder. The pulse is rapid (112-145), small and soft; the respirations are shallow, frequent (40-48), blowing and noisy—the "cerebral breathing" of Sir Dominic Corrigan.

Simultaneously with the onset of these unfavourable symptoms the eruption changes in character, becoming darker in colour and quite indelible on pressure. The spots are no longer elevated, and in the centres of many of them dark purple or bluish points appear,—the true "*petechiæ*," which Murchison defines as consisting of an infiltration of dissolved hæmatin into the tissue of the cutis. The peculiarity of typhus, so far as the rash is concerned, is that the eruption, in its earlier stage, is a true exanthem due to hyperæmia, or, it may be, congestion of the cutaneous capillaries, the outcome of "ataxic angio-neurosis" (Unna, 24), whereas in its later stages an escape of blood-pigment into the cutis from the broken-up red blood-corpuscles is substituted for this hyperæmia or congestion. The maculæ are, in a word, converted into petechiæ. Unna, however, maintains (25) that the doctrine of "blood-dissolution" in infective diseases is obsolete, and with Klebs connects the cutaneous hæmorrhages of these diseases with blocking of the vessels of the skin by bacteria. The infective forms of purpura are, according to him, most simply explained in this way; and he thinks that bacterial coagulation-thrombi will probably in future play an important part. Applying this view to typhus, the petechiæ would be the result of a diapedesis depending in its turn on clotting of plasma and consecutive stagnation round bacterial emboli.

The earlier and more marked the "typhoid state" just described, the more severe the case. The older writers spoke of it as the "putrid" or

"malignant stage." It is, however, by no means peculiar to typhus, for it may supervene in small-pox or scarlatina, and indeed in any idiopathic fever, blood-poisoning, or local inflammation.

In such a dire strait the patient may lie for many hours, or several days, until the stupor passes into profound and fatal coma, the "coma-vigil" of Sir William Jenner. In this most deadly trance the sufferer lies with his eyes wide open, with a vacant gaze and widely dilated pupils insensible to light, his lips parted, his face pallid and devoid of all expression, the pulse rapid and feeble or imperceptible, the breathing hardly to be detected, the skin cold and clammy or bathed in sweat. Although awake the patient is insensible, and surely dies. In other cases sudden engorgement of the lungs, with asphyxia, supervenes, or the heart fails, with coldness and lividity of the surface, and profuse sweating; death ensues from syncope and coma combined. Or again some fatal complication may seize and carry off its victim—a widespread bronchial effusion, it may be; or the so-called hypostatic congestion of the lungs, or laryngitis, or inflammation or degeneration of the kidneys with uræmic convulsions, or gangrene in its varied forms of bed-sore, spontaneous gangrene from arterial thrombosis, and noma or cancrum oris (gangrenous stomatitis).

Happily, such is not always or even frequently the end of an attack of typhus. Usually on or about the fourteenth day there is a more or less sudden and rapid improvement in the patient's condition, and the *stage of defervescence or crisis* ensues. At the time named the patient falls into a quiet and prolonged sleep, from which he awakes, it may be, at first bewildered and confused. Soon, however, he recognises those around him, and for the first time is conscious of his profound weakness. The pulse beats less quickly and the temperature falls, the tongue becomes moist and clean at the edges, the skin is moist or the bowels are relaxed, or the urine deposits urates in abundance and is copiously secreted. In few acute diseases is crisis so marked as in typhus, and in uncomplicated cases the final defervescence, as recorded by the thermometer, is, to adopt Wunderlich's expressive phrase, usually "precipitous."

Once the temperature falls, restoration to health, or the *stage of convalescence*, goes on apace. The tongue cleans and is moist, the appetite may become ravenous (bulimia). Meanwhile the bodily powers improve day by day, so that in three or four weeks health and strength may be fully restored. Typhus but rarely lays the foundation of any permanent organic disease.

The **mean duration** of 500 uncomplicated cases ending in recovery was, according to Murchison, 13·43 days. That of 100 fatal cases was 14·6 days. When life was prolonged beyond twenty days the fatal result, in the same author's experience, was due to some complication. T. J. Maclagan investigated 581 uncomplicated cases which recovered in the Dundee Royal Infirmary, and found their mean duration to be 13·39 days—a value which is practically identical with Murchison's estimate. Although the duration of typhus is thus about fourteen days,

this fever may run a much shorter course. Malignant cases may terminate fatally on the second or third day, or even in a few hours. To such cases the name of *blasting typhus* or *typhus siderans* has been given. This terrible form is apt to prevail in times of war and destitution.

In ordinary times, however, cases of short duration—particularly among children—are not uncommon and are usually mild. Some of these patients shew but little rash, though Murchison gives details of cases with eruption which terminated on the tenth or even as early as the eighth day.

Relapses are extremely rare in typhus. Not a single case of true relapse was ever seen by Sir William Jenner, A. P. Stewart, or Murchison. Out of 18,268 cases of typhus reported at the London Fever Hospital during twenty-three years, only one example of a true relapse was observed (by the late Sir George Buchanan); in several instances, however, a genuine has been preceded by an abortive attack. Buchanan's case was that of a nurse in the hospital, aged 42, who passed through an attack of typhus lasting two weeks. After a week's interval a relapse took place, with a recurrence of the rash, lasting upwards of a fortnight. A very similar case was recorded by W. Ebstein in 1869. In this instance an interval of twenty-five days occurred between the two attacks. Curschmann, commenting on the extreme rarity of relapses in typhus, reports two instances of what he believes were undoubted examples of relapse, adding, that he looks on the cases as anomalous, because both occurred in 1878 among a very small number of patients in the Moabit Hospital, Berlin, while in 1879 his colleagues and he failed to observe anything in the least resembling a relapse or a recurrence. The first case reported by Curschmann was that of a labourer, aged 26, whose fever terminated by lysis between the eleventh and seventeenth days. On the twenty-sixth day the temperature rose again, the spleen became enlarged, and on the day of the "relapse" there was a distinct, though scanty, eruption of rose-spots on the abdomen and chest, with a few spots on the extremities, the rose-spots "later in part undergoing a petechial transformation." This was in 1879. We have a shrewd suspicion that Widal's test would have given a positive result had it been then practised. The second example of "relapse" in typhus is equally inconclusive.

Temperature.—No clinical description of typhus would be complete without an account of the behaviour of the temperature in the disease.

A sudden rise of the thermometer takes place at the outset, culminating in a fastigium or acme of 103° to 105° F., at some time between the evening of the fourth day and the seventh day, or later. Except in severe cases, this is followed by a more or less pronounced remission of fever or *pseudo-crisis* early in the second week, generally between the seventh and tenth days. In mild cases this fall of temperature at the beginning of the second week may prove complete and final, a true crisis cutting the fever short ("typhus levissimus," or "mild typhus"). On the other hand, in grave cases a gradually rising temperature at this very period may culminate in fatal hyperpyrexia (105·8°-109·4° F.).

In many instances the pseudo-crisis at the beginning of the second week is succeeded by a second fastigium on or after the eleventh day. In favourable cases this does not attain the height of the initial fastigium in the first week. This second rise of temperature may be absent, the thermometer gradually falling through the second week until the fourteenth day, when it rapidly sinks to or below normal.

In a majority of cases defervescence is sudden. It may be preceded by a final evening exacerbation on the twelfth or thirteenth day,—a "critical perturbation," as Wunderlich called it. The descent of the temperature is then rapid, even precipitous, falling 3° to 5° F. or more in a single night, afterwards it rises some 2° in the evening, and finally reaches the normal point for the first time next morning. Such is the crisis of typhus. In its suddenness and completeness it closely resembles the abrupt defervescence in both measles and acute pneumonia (pneumonic fever), except that it occurs at the end of the second instead of the first week of the fever, as in the latter diseases.

Severe cases, with cerebral symptoms (ataxic typhus), shew a continuously high range of the thermometer without any remission about the seventh day—indeed, the thermometer continues to rise through the second week. This is especially so when some complication is threatening, a state of things which may postpone defervescence indefinitely, or usher in a fatal excessive fever or hyperpyrexia.

On the other hand, in adynamic cases, with heart-failure and pulmonary obstruction, the range of temperature may be moderate—not exceeding 103° F.—or irregular with "spiking" readings; or the fever may be continuous without morning remissions; or a fall of temperature may be observed with a rise of pulse-rate without any general improvement.

Rosenstein, in 1868, drew attention to the occurrence in not a few cases of marked precritical variations in the temperature curve, the final subsidence of the fever being preceded by a period lasting two or three days, during which the temperature swings daily through many degrees, low morning readings being succeeded by very high evening ones. Curschmann mentions such a case and gives the chart. The patient, an apprentice aged 17, passed through moderately severe typhus, in which the thermometer ranged through many degrees from morning to evening after the thirteenth day, the final critical defervescence being postponed to the seventeenth and eighteenth days.

Fatal cases are usually accompanied by high readings of the thermometer from the outset, yet even in these cases it is not so much the intensity as the continuance of the fever which determines the mortal result. Just before death and in the death-agony a supreme rise of the thermometer is a constant and ominous phenomenon. On the other hand, Curschmann reports a case in which a terminal temperature of 33° C. (91·4° F.) was recorded. The patient, an intemperate vagabond aged 23, succumbed early on the twelfth day of his fever.

Afebrile typhus has occasionally been observed. Combemale (4)

reported a case in which the temperature rose to 104° F. on the third day, then fell, and on the morning of the sixth day reached 92·6° in the rectum. The patient died next day with a temperature of 97·8°. A second patient had a temperature of about 100·4° only at the beginning of his illness; it then sank to between 96·8° and 98·6°, remained so until the ninth day, when a descent to 91·8° took place. Then again a rise to 96·8°; death with a reading of 95·9°.

A poisonous *odour* hangs about the person and especially the skin and breath of the typhus patient after the first week. It is highly infectious. With Murchison we may speak of it as a smell *sui generis*, though Gerhard aptly described it as "pungent, ammoniacal, and offensive." It most resembles that of the air in a low, damp and overcrowded dormitory after some hours of closure. It is a musty or "mousy" smell. This typhus odour is strongest in heavy, damp weather, and where ventilation is deficient—in fact it should not be perceptible in a well-managed typhus-fever ward, where due attention is paid to thorough ventilation. Curschmann tells us that, whether it was due to the faultless ventilation he cannot say, he never noticed any specific exhalation from the typhus patients in the Moabit lazaretto. Sudamina, or sweat vesicles, local eruptions of herpes, purpuric spots and vibices are accidental manifestations (epiphenomena) on the skin in typhus. In convalescence the skin commonly peels off in fine branny scales (furfuraceous desquamation), and the hair usually falls off, although not to so great an extent as in small-pox. Interference with the nutrition of the skin and its appendages is shewn by the frequent occurrence of a transverse white band and an atrophic furrow at the lunula of the nails, four to six weeks after the commencement of the fever. These markings gradually advance to the tip of the nails during the five or six months following the attack.

Daily examination of the pulse, heart, and lungs should never be omitted in typhus. The circulation especially is much disturbed. The pulse is at first full but soft and compressible, and moderately quickened (108-120 beats a minute); or it may be abnormally slow, down to 48, 40, and even 30 beats—often a sign of debility. When the patient sits up his pulse becomes quicker and less full; in the second week it is often dicrotous or undulatory. This is an indication of very low arterial blood-pressure; and a practical bearing of the observation is that the typhus patient should never be allowed to assume a sitting, much less a standing, posture.

The condition of *the heart* is profoundly altered in this fever. Weakening of the heart generally begins about the fourth or fifth day, and passes off after the tenth day in cases which are about to do well. The muscular tissue of the organ is softened and friable. All modern pathologists agree in attributing this change to cloudy swelling and granular fatty degeneration. Those who maintain that the change is inflammatory speak of the disease as an "acute parenchymatous myocarditis" or "an infective myocarditis." Those who regard the

condition as merely degenerative give to it the names of "acute parenchymatous degeneration," "albuminous degeneration," or "febrile softening of the heart." In it the heart is sometimes perceptibly dilated; the myocardium is of a dirty greyish-red or greyish-yellow colour, with occasional extravasations; its consistence is soft; its substance is lax, flabby, and friable. Thrombi may be found in the ventricles. Microscopically the muscular fibres are swollen, their striation is more or less lost and replaced by granules (albuminous) and fatty molecules; occasionally they undergo hyaline degeneration (Zenker). Along with these evidences of degeneration there are found certain appearances which suggest regeneration—a condition certainly established in favourable cases of typhus.

This acute parenchymatous change may be the result of the specific action of the febrile poison, of the accompanying pyrexia, or of both, on the protoplasm (Mitchell Bruce). As regards the symptoms, cardiac failure is the chief evidence of this morbid condition of the myocardium. We are indebted to Stokes for a full clinical account of this febrile weakening of the heart. According to him the first objective symptom is a diminished cardiac impulse, even when the patient lies partly on the left side, in which position the apex of the heart comes into contact with the chest-wall. The impulse, in the next degree, fails altogether, while the first sound becomes fainter or less loud. Occasionally a temporary murmur accompanies this sound. These signs are most apparent towards the left, because the left ventricle is most affected. In the third stage of the lesion the first sound disappears, the heart being heard to beat with only one, and that the second sound, which may be actually accentuated from increased pressure in the pulmonary artery, or appear accentuated by contrast. In a yet more advanced stage of cardiac weakness both sounds are equally diminished in loudness and become equidistant, while the heart beats with great rapidity (tachycardia). The pulse-rate is now from 140 to 160 beats per minute. To this state the term "fœtal heart" has been applied, because in its weakness and from its quickness at the expense of the long pause it resembles the heart-beat of the fœtus in utero. This condition indicates great debility. The last stage of all is silence of the heart, a sign of impending dissolution, a condition which, as Stokes observes, is almost always fatal.

In making a physical examination of the heart allowance must be made for the muffling of the sounds under the influence of a very muscular or a very fat chest-wall, or in the presence of loud bronchial râles and rhonchi.

Should the patient recover, the physical signs alter in the inverse order. Coincidently with the return of the first sound the pulse should fall in rate, otherwise the prognosis is bad. After the fever the pulse often falls much below the normal rate—even as low as thirty beats in the minute. It then slowly recovers itself.

In typhus, when there is no pulmonary complication of account, and when the nervous symptoms are not pronounced, the normal ratio of the

respiration to the pulse—1 to 4—is maintained. Thus a pulse of 120 beats per minute would mean thirty respirations. In grave cases, however, certain *abnormal modes of respiration* may arise from cerebral disturbances, independently of any pulmonary disease. In such cases the breathing is hurried, sighing, irregular, spasmodic or jerking. There is a *besoin de respirer*, what the Germans call *Lufthunger.* This irregularity of breathing, independent of any pectoral affection, Graves called "cerebral respiration." In other cases the breathing is irregular, blowing or hissing, while the mouth is kept closed, the cheeks puff out, and the nostrils dilate with each expiration; this is the "nervous or cerebral respiration" of Sir Dominic Corrigan. A third variety is the rising and falling breathing, called "Cheyne-Stokes' respiration."

Hypostatic congestion very often takes place in the most dependent parts of the lungs. Its causes are—impaired innervation (paresis of the pneumogastric nerves), impaired nutrition of the blood-vessels, and lessened heart power. The occurrence of this serious complication is favoured by the greatly impaired movement of the chest-walls and the dorsal decubitus, in which the patient lies on the broad of his back. Physical examination of the chest day by day affords timeliest warning of the stealthy approach of this perilous condition, and should never be neglected in typhus. There may be neither cough nor expectoration, but the rapid laboured breathing with cyanosis due to defective aeration of the blood should draw the attention of the physician to the patient's danger from serous œdema of the lungs. The physical signs may be those of a widespread bronchial catarrh.

The breath of a typhus patient is offensive, heavy and pungent, often ammoniacal. Its smell has been likened to that of yeast. The absolute quantity of carbonic dioxide in the lungs is increased, but the proportion of this gas in the expired air is considerably below the normal amount. This anomalous result, arrived at by Dr. A. Malcolm of Belfast in 1843, is explained by Vierordt's observation that, even in health, the proportion of carbonic acid in the expired air diminishes as the respirations become quicker.

Bronchial catarrh may usher in, accompany, or succeed an attack of typhus. It is a dangerous complication, particularly in winter—first, because it is almost certain to be associated with more or less hypostatic consolidation in the lungs; secondly, because the bronchial secretion is likely to accumulate in the tubes and asphyxiate the patient in consequence of his inability to cough, coupled with the impaired nutrition and paralysis of the muscular fibres of the bronchi. Pneumonia is a rare complication or sequel of typhus. It may be distinguished from hypostatic congestion (with which, however, it is sometimes associated) by the unilateral dulness, and by the presence of tubular breathing and rusty sputa. Pulmonary gangrene is a rare but fatal complication, which is apt to occur in very destitute patients. It may be of embolic origin, secondary to extensive bed-sores over the sacrum, as in cases observed by Murchison. Lastly, it may result from aspiration of septic

detritus in laryngeal perichondritis (Curschmann). Pleurisy, with purulent effusion, is a rare and may be a latent complication. Tuberculosis of the lung also is an infrequent sequel of typhus, although it is by no means uncommon after enteric fever.

As regards *the urinary system*, the amount of urine is much diminished at first, when it is acid, dark-coloured from typhous dissolution of the blood, and of high density (1024-1036). Urea is increased in quantity at the outset, but afterwards falls below normal, on account of low diet and imperfect elimination. Albuminuria is often present, but this does not necessarily imply renal disease; for in excessive blood-changes such as occur in bad typhus the blood-serum may find its way into the urine. From experiments undertaken by H. Lorenz it seems probable that the albuminuria of fever depends directly on certain histological changes in the renal epithelium. Acetone may be present in variable proportion, and in children diacetic acid and also β-oxybutyric acid (von Jaksch). Diaceturia in children is not an unfavourable indication, but in adults it is a grave sign, and is not infrequently followed by fatal coma in fever as well as in diabetes mellitus. Uric acid is usually increased, and both Frerichs and Murchison detected leucin and tyrosin in the urine of typhus. Chlorides gradually lessen in amount from the first. Towards the close of the fever there may be diuresis—a recognised mode of crisis—with a copious precipitation of urates. General convulsions are most dangerous in typhus; they occur in about one per cent of the cases, and with rare exceptions are of uræmic origin. In most of these cases there is albuminuria, with scanty or suppressed excretion. Kidney disease is often present or there may be a history of intemperance. Uræmic convulsions do not usually appear before the middle or end of the second week. Murchison took notes of sixty-nine cases of convulsions in typhus. Of these, sixty-one were fatal, and only eight recovered. Occasionally simple retention of urine determines an attack of epileptoid convulsions, in which case judicious treatment may afford immediate relief. The catheter should be passed, as recommended by Stokes, after a few whiffs of chloroform cautiously given, if this be necessary.

Convulsions are commonly preceded by drowsiness or delirium. Allusion has more than once been made to the important part played by *the nervous system* in the symptomatology of typhus. Frontal headache is an early and constant symptom. It is a dull, aching, heavy pain —rarely acute, darting, stabbing, throbbing, or bursting. It is the most characteristic nervous symptom during the first week, when, however, vertigo and rheumatoid pains in the back and limbs may also be troublesome. Other sensory disturbances are the occasional occurrence of severe neuralgic pains in certain nerve-tracts during defervescence (Curschmann). Anæsthesia of the same areas may appear, lasting long after recovery. Curschmann has known anæsthesia of an area on the thigh as large as the palm of the hand to persist for three months after recovery, and a similar one in the distribution of the ulnar nerve to last for two months after recovery.

Mental confusion or actual delirium takes the place of headache towards the close of the first week; hence typhus has often been called "brain-fever." The mind becomes blunted and dull, memory lapses, and cerebration is slow and defective; in this state the term "typhus" becomes singularly appropriate. The delirium varies in character, as has been already stated. Of the three types—typhomania, delirium tremens, delirium ferox—the first is the most common, the last is the least common. "The mental state of the delirious typhus patient," wrote Murchison, "is peculiar, and well worthy the study of the metaphysician. As a rule the memory is first and most affected; judgment and power of connected reasoning often remain after the memory has entirely gone. The mind may labour under the strangest delusions, and often it appears to revolve obstinately around some fixed idea. The patients rave about objects which have greatly engrossed their attention, either immediately preceding the attack, or years before, and which are now jumbled with persons, scenes, and events with which they have had no connection." One of Curschmann's patients, a lawyer, of a naturally vivacious disposition, exhibited during the fever so violent an antipathy towards his male attendant that the man's life was in danger. After his recovery the patient remembered distinctly the details of the terrifying apparition which had so strangely excited him in his illness. To this disordered imagination the man sometimes appeared to have enormously long arms or legs, sometimes he seemed to inflate himself to frightful proportions, or sat without any head by his bedside. The apparition was so appalling at one time as to induce him to attack the monster with a knife, as the patient himself afterwards remembered.

Wakefulness is a common symptom in early typhus. It is apt to be followed by extreme nervous agitation and prostration, or by somnolence, deepening into complete coma and terminating in death.

Various muscular paralyses are observed in the course of the fever. Paralysis of the neck of the bladder, coming on about the tenth or eleventh day, leads to involuntary dribbling of urine; paralysis of the sphincter ani, to incontinence of fæces. The coats of the bladder may lose their power from over-distension, causing retention of urine, and incontinence and retention may even co-exist. Meteorism is due to paresis of the walls of the intestines. The orbiculares palpebrarum may lose their power, so that the patient cannot close his eyelids, and keratitis and even sloughing of the cornea are induced from exposure. Aphonia, inability to protrude the tongue, and dysphagia are other examples of paralyses induced by typhus—the last-named being the worst of all, and usually the forerunner of death.

Muscular agitation indicates great prostration, and is of grave import. It is observed in patients who are old and infirm, or intemperate, or brain-workers. Its forms are: tremulousness of the hands, tongue, or whole body; rapid oscillatory movements of the eyeballs (nystagmus); choreiform movements of the extremities; choreic convulsions; twitching of the tendons of the wrist (subsultus tendinum) and of the facial muscles;

picking at or fumbling with the bed-clothes (floccitatio or carphology); and obstinate hiccup (singultus).

Muscular rigidity is much rarer than muscular agitation, although equally unfavourable; the fingers may be clenched, or the forearms flexed. There may be tonic spasms of certain muscles, or even trismus or strabismus. Well-marked opisthotonos, with the head bent back and the limbs rigid, was once observed by Murchison and once by Perry—both cases proved fatal. Of general convulsions I have already spoken.

The *organs of special sense* suffer in proportion to the severity of the fever. The suffused conjunctivæ and contracted pupils—"pin-hole pupils" of Graves—constitute "the ferret eyes" of typhus. In coma the pupils dilate and become insensible to light, with squinting. Inequality of the pupils has frequently been observed by Dr. Cayley, who regards the phenomenon as without prognostic significance. Photophobia is sometimes noticed. Tinnitus aurium and noises in the head are often present at the beginning and close of the fever. Deafness is commonly observed; if bilateral, it is probably part of the general anæsthesia of the fever, or it may be due to typhous softening of the intrinsic muscles of the ear (Stokes), or to swelling of the mucous membrane lining the Eustachian tubes, or otitis may cause it. This last may proceed from catarrh of the tympanum; it may assume the form of a purulent otitis media, leading to perforation of the membrana tympani, inflammation of the labyrinth, or purulent infiltration of the mastoid cells, requiring surgical treatment if we would save the patient from thrombosis and inflammation of the cerebral sinuses and metastatic or septic pneumonia. Intolerance of sound is a distinctly bad sign. The senses of smell and taste are often blunted or obliterated. Epistaxis is very rare in typhus.

The sensibility of the skin is usually lessened (hypæsthesia), impaired (paræsthesia), or entirely lost (anæsthesia); hyperæsthesia is occasionally observed. So far no instances have been recorded in which typhus has been followed by that linear atrophy of the skin, with or without hyperæsthesia of adjacent parts, which is a rare sequel of enteric fever, and which has been described by Sir Dyce Duckworth, Sir S. Wilks, Dr. Shepherd of Montreal, Dr. T. R. Bradshaw of Liverpool, and several continental observers.

The chief determining causes of **the complications** which modify the course of typhus more or less unfavourably are—(i.) The weakened state of the heart; (ii.) the impure state of the blood; (iii.) constitutional peculiarities and family idiosyncrasies; and (iv.) the so-called "epidemic constitution" at a given time or place—that is, the special characters of the prevailing epidemic.

The complications which affect the respiratory organs are—(i.) *Laryngitis*, infrequent but dangerous, catarrhal or membranous in character, or shewing itself as acute œdema of the glottis, and giving to this fever the name of laryngotyphus (Rokitansky)—*perichondritis laryngea* in not a few cases affects one of the arytænoid cartilages, which may ulcerate or become separated from its attachments (necrosis); in one case, observed by

Curschmann, detachment took place and the cartilage was expelled when the patient coughed; (ii.) *Bronchitis*, a very common and dangerous complication or sequel; hence the names "Catarrhal typhus" (Irish writers), "Bronchotyphus" and "Pneumotyphus" (Rokitansky); (iii.) *Hypostatic congestion* of the lungs, already described; (iv.) True *pneumonia* (*vide* p. 550); (v.) *Gangrene of the lung* (*vide* p. 550); (vi.) *Pleurisy*, rare and latent, but with purulent effusion from the outset; (vii.) *Tuberculosis* of the lungs, a rare sequel; and (viii.) *Hæmoptysis*, exceptional, and resulting either from tuberculosis, pulmonary apoplexy, or from acute hæmolysis (Murchison).

As to the blood and circulatory organs, typhus, like small-pox, may so devitalise and defibrinate the blood as to establish—(i.) an *acute hæmophilia*, the patients becoming "bleeders" from "typhous dissolution of the blood," or from bacterial thrombosis as already explained. Hence the formation of purpuric spots and vibices, and the occurrence of epistaxis, hæmoptysis, hæmatemesis, melæna, menorrhagia, hæmaturia, and other hæmorrhages. (ii.) *Pyæmia*, with purulent deposits in the joints, is a rare and fatal complication at the time of crisis or later. It is signalised by repeated rigors, unstable spiking temperature ranges, extreme prostration, heart-failure, jaundice, and profuse sweating. (iii.) *Venous thrombosis*, an occasional sequel, causing phlegmasia alba dolens, or "white leg." This condition may also result from obstruction of the lymph-channels or inflammation of the subcutaneous areolar tissue (diffuse cellulitis). (iv.) *Arterial thrombosis and embolism* are occasional but serious complications or sequels. They cause local gangrene, cancrum oris, necrosis of bone, abscess or gangrene of the lungs, and splenic infarctions. Lastly, in the heart itself (v.) an *acute granular disintegration of the muscular tissue* often takes place, constituting a dangerous lesion, especially in advancing life; but pericarditis and endocarditis are extremely rare.

Profound though the influence of the poison of typhus is upon the nervous system, yet tangible pathological changes and complications connected with that system are infrequent. The cerebral symptoms of this fever are usually, perhaps almost invariably, independent of inflammation of the brain or its membranes. Nevertheless, *meningitis*, although rare, is met with in typhus, of which disease also *temporary fatuity* and *mania* are infrequent and very sad sequels. Happily recovery generally follows at last, usually in two or three months. As to meningitis, Hampeln reports 4 cases of purulent meningitis out of a total of 726 patients in an epidemic at Riga. *Paralysis* is a rare sequel. It commonly assumes the form of hemiplegia, but may occur as paraplegia or as general paralysis (H. Kennedy). Hemiplegia may be caused by cerebral hæmorrhage, embolism, or thrombosis. Hampeln has described one case of thrombosis of the left middle cerebral artery. *Peripheral neuritis* may be the serious cause in some instances of the muscular pains which sometimes occasion much distress in convalescence, and even protract recovery. The knee-jerk or "patellar reflex" is sometimes exaggerated; and ankle-clonus is sometimes found in convalescence.

Lesions of the digestive tract are not common in typhus. *Erysipelas of the pharynx* may cause dysphagia or œdema of the glottis, and so endanger life. *Hæmatemesis* and *intestinal hæmorrhage* are rare but fatal complications: they result in the graver cases of typhus from the liquefied state of the blood. Curschmann mentions the case of a young man treated in the Moabit Hospital, Berlin, in 1879, who had a profuse intestinal hæmorrhage on the ninth day of a severe attack of typhus—at the autopsy the source of the bleeding was found in a duodenal ulcer which was evidently of long standing. *Diarrhœa* and *dysentery* are occasionally met with—the latter complication in camps and sieges. *Jaundice* is infrequent, but fatal: of fifteen instances observed by Murchison, the jaundice was due to consecutive congestion of the liver in three cases, to gastro-duodenal catarrh in one case, and to some abnormal state of the blood in the remaining eleven cases, of which nine proved fatal. *Peritonitis* is almost unknown as a complication of typhus: in two cases seen by Murchison the causes were, respectively, the bursting of a softened embolic infarct in the spleen and tuberculosis of the peritoneum.

In connexion with the urinary organs *nephritis* is a dangerous complication, often inducing fatal uræmic convulsions. *Cystitis* may result during convalescence from retention of urine and over-distension. Both of these affections may be accompanied by hæmaturia, which may also arise from acute hæmolysis. Curschmann saw a single case of unilateral orchitis in a young man shortly before the crisis; it lasted ten days and subsided without going on to suppuration. He observed that most writers do not even mention orchitis as a complication of typhus.

The integuments and bones may suffer severely, as in enteric fever. *Bed-sores* are favoured by impaired innervation, but arise directly from pressure, early neglect, and want of skilled nursing. *Spontaneous gangrene*, independently of pressure, is probably brought about by arterial thrombosis; it affects the toes and feet, the nose, penis, scrotum, and female pudenda. It occurs in badly-fed patients, and is ushered in by severe shooting pains, numbness, coldness, and lividity. *Gangrenous stomatitis* (noma, or cancrum oris) is a destructive and fatal variety of gangrene, which attacks the cheek, mouth, tongue, and face of delicate, badly-fed children towards the close of the fever. "*Hospital gangrene*" attacks wounds and abraded or ulcerated surfaces in persons under the influence of typhus. It is identical with or closely allied to acute sloughing phagedæna. Owing to improved hygiene these septic complications of typhus have now only a historic interest. *Inflammatory swellings* or *buboes* are not infrequent at or after the crisis, especially in the parotid and submaxillary regions. These bubonic swellings may terminate in purulent abscess, or recede without suppurating; they are a formidable complication in the former case.

Lastly, typhus fever may be complicated by the co-existence or close sequence of such other specific diseases as small-pox, scarlatina, diphtheria, erysipelas, and enteric fever.

The following, among many other varieties of this fever, have been

described :—(i.) Inflammatory typhus, characterised by much febrile reaction in the young and robust, and in patients of the upper class; (ii.) Nervous or ataxic typhus ("brain fever"), in which nervous symptoms predominate and the rash is copious, dark, and petechial; (iii.) Adynamic typhus, accompanied by great muscular and cardiac prostration, involuntary evacuations, and a tendency to collapse; (iv.) Ataxo-adynamic typhus —congestive typhus—by far the most common variety; (v.) Typhus siderans, or "blasting typhus," very acute and most fatal; (vi.) Typhus levissimus, or "mild typhus"; (vii.) Abortive typhus in the "*typhisation à petite dose*" of Jacquot, in which symptoms occur in persons exposed to infection without developing into actual typhus; (viii.) Catarrhal typhus, an Irish appellation for the disease, because it is so often complicated with bronchial catarrh. For this reason also Rokitansky devised the names "bronchotyphus" and "pneumotyphus."

Diagnosis.—The rash is pathognomonic. Before it appears we have grounds for a differential diagnosis in a history of exposure to the infection of typhus, and of such symptoms after exposure as rheumatoid pains, headache, and early prostration. It may be necessary to distinguish typhus from the following diseases or diseased conditions, or vice versa :—

1. Spirillum fever (relapsing fever (*vide* vol. i. pp. 1186, 1188)).—In forming an opinion regard should be paid to the nature of other cases of fever in the same house or family. In relapsing fever there is no rash, while epistaxis, jaundice, vomiting, and cardiac murmur are common phenomena. The febrile attack terminates by a critical defervescence after five or seven days. This is followed by a remission lasting seven or eight days, and by a relapse on or about the fourteenth day, lasting some three days. This fever prevails epidemically, for the most part during seasons of scarcity and famine. The spirillum is to be found by appropriate means. [Cf. "Spotted Fever" in vol. on Tropical Diseases.]

2. Enteric or typhoid fever, in contrast to typhus, begins insidiously, is often accompanied by diarrhœa, lasts at least ten days longer (twenty-four compared with fourteen days), terminates by lysis, has an unchangeable eruption—if any—of circular, lenticular rose-spots, which never become petechial, and which fade after death. In hæmorrhagic typhoid, it is true, petechiæ may appear. Enteric fever also is characterised in general by a clear complexion, bright eyes, dilated pupils, comparatively moderate prostration; tenderness of the abdomen, tympanites, *gargouillement*, or gurgling in the ileo-cæcal region; early epistaxis also is common, and the pathological changes are specific, being found chiefly in the last few inches of the ileum and about the ileo-cæcal valve as well as in the mesenteric glands and the spleen. Bacteriological examination will reveal the presence of Eberth's bacillus in the excretions, and the agglutination test will establish the diagnosis of enteric fever.

3. Tropical remittent fever (jungle fever) is a parasitic disease, caused by protozoa (Laveran) in the blood. It arises independently of overcrowding, prevails in tropical climates and in warm and rainy seasons.

The spleen is much enlarged, and quinine often acts specifically. Petechiæ may no doubt be present, but the macular rash of typhus is wanting.

4. Purpura is non-contagious, and, as a rule, apyrexial. It is unaccompanied by cerebral symptoms, but is attended with hæmorrhages from the mucous membranes. The spots are larger than the petechiæ of typhus.

5. Measles presents a characteristic history and epidemic prevalence. It is further distinguished by its prodromal catarrhal symptoms, the brighter tint and greater abundance of its rash, the frequent presence of diarrhœa, and its early defervescence. Its victims are usually children, who enjoy a comparative immunity from typhus.

6. The initial symptoms of small-pox closely resemble the onset of typhus. The backache of small-pox is of some slight value in diagnosis, but a more important diagnostic is the early appearance of a scarlatinal rash on the thighs and arms, which strongly points to small-pox. In that disease also the true rash first shows on the face, a part which escapes in typhus.

7. In inflammation of the brain (cerebritis or encephalitis) or its membranes (meningitis) there is early delirium with excruciating headache. The senses are morbidly acute. The pulse is bounding. There is no rash like that of typhus. In meningitis loud cries or screams (*cri cérébral*) occur, also strabismus, ptosis, opisthotonos, and partial palsy. There is extreme intolerance of light (photophobia) and of sound. Nausea and vomiting are common. A sign of dubious value is the persistence of a red streak upon the skin after pressure by the finger-nail (*tache cérébrale*).

8. The delirium tremens of the drunkard sets in with sleeplessness and delirium, without shivering, headache, or pains in the limbs. The tongue is moist and coated with a creamy fur, the skin is damp and cool. There is no eruption, and the temperature is not high.

9. Asthenic or typhoid pneumonia is distinguished, at any rate after the first day or two, by the presence of physical signs in the lung and the absence of eruption.

10. Uræmia chiefly occurs in chronic interstitial nephritis in middle or advanced life, especially in gouty subjects or persons suffering from chronic lead poisoning, and the temperature is normal or subnormal. This last circumstance Murchison calls "the grand point of distinction." Finally, although the "typhoid state" may be fully developed in uræmia, the typhus rash is, of course, wanting; other rashes, however, may occur in uræmia (14).

Prognosis.—The unfavourable signs in a given case of typhus are—1, a presentiment of death, often entertained by physicians when ill of typhus; 2, a soft and compressible pulse, in rate above 120 in an adult; 3, absence of cardiac impulse, and lessened or inaudible first sound of the heart; 4, hurried respirations, particularly if no pulmonary lesion exist to explain this symptom; 5, sleeplessness and delirium; 6, complete coma-vigil of Sir William Jenner; 7, the presence of the pin-hole

pupil of Graves; 8, great prostration; 9, convulsions; 10, muscular tremors and hiccup; 11, relaxation of the sphincters before the tenth day; 12, tympanites or meteorism; 13, lividity of the face and surface generally; 14, abundance and darkness of the rash; 15, persistent high temperature; 16, profuse sweating after the tenth or twelfth day; 17, the presence of any serious complication; 18, a general hæmorrhagic tendency or acute hæmophilia ("Faulfieber").

When death does take place it results from asthenia, with heart-failure; or from ataxia, nervous symptoms deepening into coma; or from some intercurrent complication or sequel.

Mortality.—The death-rate from typhus among the community at large probably does not exceed 10 per cent of those attacked. Hospital statistics shew a higher rate. At the London Fever Hospital, in twenty-three years ended 1870, the death-rate was 18·92 per cent. At Cork Street Fever Hospital, Dublin, in the last epidemic, that of the years 1880-82, the death-rate was 10·5 per cent. As in the case of other epidemic diseases, the mortality is greater immediately after the outbreak than in the later periods. During the twenty years ended March 31, 1891, 2895 cases of typhus were admitted to Cork Street Fever Hospital, Dublin. Of these, 363 proved fatal, the death-rate being 12·6 per cent, or nearly 1 in 8. Age influences the fatality of typhus in a most remarkable way. At the London Fever Hospital, among 18,138 cases, the mortality during the first five years of life was 6·69 per cent; in the second lustrum it fell to 3·59; between 10 and 15 it was only 2·28 per cent; between 15 and 20 it rose to 4·46. Of the patients above 30 years, 35·39 per cent died; above 40, 43·48; above 50, 53·87; above 60, 67·04; above 70, 79·00; and above 80, 100·00 per cent. And yet typhus is not invariably fatal in very advanced life, for in 1821 a man, said to have been aged 104 years, recovered from petechial typhus in the wards of Cork Street Hospital. Sex influences mortality; men die in greater numbers than women. The intemperate, the sickly, the obese, or the very muscular, the hard-worked, whether bodily or mentally, but especially the latter, run the worst chance of all if attacked by typhus. Season affects the death-rate, which drops to a minimum as summer advances; but rises to a maximum in late winter and spring, which increase is probably due to concentration of the poison in closer rooms. Fatigue and privation, and particularly too late removal to hospital, are all prejudicial to the typhus patient. Pregnancy adds little to the danger of this fever, but suckling induces anæmia, and increases the risk of death from exhaustion.

Treatment.—In the recognition that destitution, overcrowding, and deficient ventilation vastly increase the predisposition to typhus, lies the key to the preventive treatment or *prophylaxis* of the disease. Personal cleanliness, an abundant supply of good, wholesome food, strict temperance, a sufficient cubic air-space per head of the population (at least 500 cubic feet), and free ventilation, which means the supply of 3000 cubic feet of fresh air per head every hour, are the best

preventives. Those sick of typhus should be carried to hospital in suitable ambulances—never in public conveyances, and while in hospital they should be treated in large airy wards or rooms, 1500 to 2000 cubic feet being allowed to each patient, and the beds should be at least six feet apart. If the hospital has more than one story, the typhus wards should be at the top of the building, as the poison is light and volatile. Free ventilation is essential; indeed, whenever the weather permits, a strong current of fresh air should be allowed to blow over and around the typhus patient (1). In summer and autumn the typhus cases are best treated in the open air, of course protected against sun and rain. The open-air treatment has a most beneficial effect on the nervous system, allaying delirium and inducing sleep. Even in winter but little risk of catching cold exists while the fever lasts; and there is good reason to believe that an abundant access of fresh air may positively control the bronchial catarrh and other pulmonary affections of typhus, which result not from cold, but from passive hyperæmia of the bronchial mucous membrane and of the parenchyma of the lungs; lesions which really belong to the more essential pathology of the disease.

Bearing in mind the early and grave prostration of typhus, the patient, having been bathed and thoroughly cleansed, should take to bed as soon as possible in a cheerful, large, airy apartment with two bedsteads in it, one for day and one for night. The best form of bed is a hair-mattress laid upon a woven wire spring-mattress. The bed-clothes should be light and frequently changed. Curschmann reminds us that mirrors, wall-paper of glaring design, conspicuous pictures, and any other brightly coloured or otherwise unpleasantly prominent objects should be covered or removed, for their presence feeds the disordered imagination of the delirious patient, increasing his hallucinations, and exciting him to the point of mania. The patient's head should be kept as cool as possible, but his feet should be warm. There is no disease in which the services of a trained, experienced, strong, and judicious nurse are more needed than in typhus. Both in hospital and in private practice the nurse or nurses, for there should be a day-nurse and a night-nurse, should keep a written record, at stated intervals previously arranged, for the information of the physician, of the times at which food and stimulants have been given, the bowels have moved or water has been passed, of the changes in the nature and character of the symptoms from visit to visit of the physician, and of the behaviour of the temperature and the rate of the pulse and respirations. In all bad cases, with profuse eruption, the entire surface of the body should be gently sponged twice or three times a day with equal parts of vinegar and warm or tepid water.

So far as the physician himself is concerned, every case of fever should be visited at least twice a day—morning and evening—during the acute and critical stages; for a few hours may mean life or death to the sufferer, and again, a morning visit only may give a very false impression of a patient's state and prospects. The condition of the heart and lungs, of the kidneys, and of the bladder, should always be investigated.

The medical treatment of typhus is purely symptomatic, for as yet we possess no specific for this disease, if we except fresh air. While we endeavour to sustain the vital powers of the fever patient by appropriate food and stimulants, we should avoid anything which would cause congestion, or put an additional strain on organs already overtasked and with impaired functions.

The food should be both nutritious and digestible, consisting of such articles as milk, eggs, beef-tea, veal broth, chicken broth, mutton broth, (strained), meat essences, meat jellies, arrowroot, sago, tapioca, bread and milk, junket, wine-whey, and egg-water, butter-milk, fermented milk (Kephir), custard, tea or coffee well diluted with milk. If there be a tendency to diarrhœa the milk should be boiled, or lime water should be given with it in the proportion of one part in four, or vermicelli, gelatin (isinglass), or arrowroot should be added to the milk or broth. If the digestive powers are very weak the food may be peptonised.

Food should be given to the fever patient at regular intervals—every three hours, every two hours, or even every hour; but the stomach should be allowed to rest for at least the last-named interval, else nausea, vomiting, flatulence, and diarrhœa may be caused through non-assimilation and decomposition of the food. When a patient remains in a state of stupor he should be roused from time to time to take food; a teacupful of black coffee is often most beneficial. If the patient fall into a tranquil sleep after a period of wakefulness, nervous excitement, or delirium, he should not be aroused for food. In delirium, or when the patient is unconscious or unable to swallow, liquid nourishment should be given by the nasal tube, or nutrient enemas should be administered. In the latter case the rectum should first be washed out by a clyster of warm water, and then an enema should be given of milk and brandy, or beef-tea, or egg-flip, at a suitable temperature (100° F.), and of moderate volume (not exceeding four to six ounces).

Very few fever patients can digest more than one pint of animal broth, and from one and a half to two pints of milk, in the twenty-four hours; and these quantities seem to be a fair allowance for an adult.

The thirst of fever is the expression of a real want in the system—it is a craving for more water. The question then arises, How may water be supplied to the typhus patient? Taken internally water is the most effectual assuager of consuming thirst, the best and safest diuretic, diaphoretic, aperient, and eliminative we can prescribe. Its administration in moderate quantities, at frequent intervals, often allays delirium and induces sleep. Another way in which water may be given is in the form of ice, sucking fragments of which is most grateful to the conscious and non-delirious patient. Ice, however, sometimes leaves a parched feeling in the mouth, and children are apt to dislike it. In such cases, it should be used to cool the beverage taken to allay thirst.

To wash out from the system the retained products of increased tissue-change in typhus is one of the most pressing indications for treatment. It is safely and efficiently fulfilled by the internal administration of

water. There can be no doubt, also, that in fever water is absorbed by the skin when tepid sponging is practised, or when the patient is placed in a warm, tepid, or even cold bath. Curschmann truly observes that the value of the bath-treatment lies not so much in the reduction of the body-temperature as in the favourable effect produced on the entire symptom-complex of typhus, particularly on certain vital centres which are especially implicated in the poisoning, namely, the respiratory and circulatory centres. This physician does not use cold baths save in special circumstances. He prefers von Ziemssen's method of gradually reducing the temperature of the bath. He places the patient in a bath of 75° to 78° F., and cools the water by degrees to 68° or 63° F., seldom lower. A cold damp cloth or an ice-cap is applied to the patient's head during the bath.

Following the practice of Dr. Stokes, at the Meath Hospital, Dublin, cold affusion may be used: the modified plan being adopted of pouring cold water from a large jug over the head and face of a typhus fever patient while lying crossways in bed, his head and shoulders being supported over a bath placed alongside the bed. The stream of water should be directed upon different parts of the head from time to time; otherwise pain may be caused. Ice also may be applied to the head—a piece, rubbed smooth with the hand, being placed in a cup-shaped sponge of convenient size. By inverting the sponge the ice is brought into contact with the shaven scalp, and is passed round and round the head by a continuous gentle motion. In this way no pain is caused, the process is grateful to the patient, and the whole head is uniformly and gradually cooled. An ice-cap may be placed on the head, but should the patient be very irritable the use of Leiter's tubes is preferable, for the patient is not then disturbed by the removal and refilling of the ice-cap.

The question of alcoholic stimulants in typhus is an anxious one. The chief indications for their use are derived from the state of the pulse, heart, tongue, and brain; from the presence of complications, and especially of the "typhoid" or "ataxic state" (that is, stupor, low muttering delirium, tremor, subsultus, involuntary evacuations, coma-vigil, etc.). Alcoholic stimulants are doing a typhus patient good if under their use—

1. The heart's action becomes stronger and less rapid, and the first sound more distinct, and the impulse increases in strength.

2. A soft, compressible, undulating, irregular, or intermitting pulse becomes fuller, stronger, and more regular in rhythm and volume.

3. A dry, brown, or black shrivelled tongue (*parrot tongue*) becomes clean and moist at the edges.

4. Delirium lessens, the patient becoming more tranquil, or even falling asleep.

Medicinal stimulants are most urgently required during the night and in the early morning, when the vital powers are wont to flag. In the forenoon they are less necessary. In cases of extreme prostration medicinal stimulants or tonics should be combined with wine or spirits; for example, carbonate of ammonium and bark, the different ethers,

camphor, musk, turpentine, quinine, and strychnine. Murchison considered, and rightly, that patients under twenty years of age do best, as a rule, without any alcohol, whereas most patients over forty are benefited by it after the first week of the fever. The effect of each dose should be carefully watched and noted; and stimulants must never be ordered as a matter of routine or without a sense of grave responsibility. Although many patients pass through typhus in safety without alcohol, there can be no doubt that its judicious use may save life. It may even be necessary to prescribe it at an early stage of the fever, in cases where the occurrence of great prostration of nervous energy is foreseen. In such circumstances the physician gives stimulants *by anticipation.* In adopting this anticipative treatment by stimulants (Stokes) we follow the old maxim, "*venienti occurrere morbo*," and we take into account the character of the prevailing epidemic and the previous medical history of the patient, and his habits as regards indulgence in alcohol.

In former days musk enjoyed a high reputation as a diffusible stimulant and antispasmodic in the low muttering delirium and nervous prostration of the ataxic state. In Ireland, however, of late years this remedy has fallen into unmerited disuse, partly because of the great cost of the drug, and partly, it is to be feared, because its exhibition was often postponed until too late to prove of much use. In an epidemic of typhus in Leeds in 1866, Dr. Clifford Allbutt found musk most valuable when given in 5-grain doses in low delirium. It may be prescribed in bolus or emulsion. Camphor may be substituted for musk in hospital practice, or these powerful diffusible stimulants may be given in combination. Among the various ways in which camphor may be administered, the method by hypodermic injection should be mentioned. A solution of camphor in almond oil, of the strength of 1 in 10 (10 per cent), may be injected subcutaneously, and will be found most useful as a stimulant, and at the same time a hypnotic and calmative. So far back as 1878, Eugene Wittich described camphor as an excellent remedy for the sleeplessness of melancholia in female lunatics. After the subcutaneous injection of 0·1 to 0·2 gramme of camphor, he found that the patient quickly became drowsy, and soon went off into a sleep of several hours' duration. He dissolved the camphor in sweet almond oil (1·0 to 10·0 grammes). The injection is less painful than one of morphine, and abscesses never occur afterwards. The hypodermic needle must be rather wide, otherwise the oil does not flow readily.

The management of some of the complications and sequels of typhus calls for a few remarks:—

Pulmonary congestion and *bronchitis* are best treated by external means —poulticing, dry-cupping, and the application of rubefacients and stimulating liniments, like compound camphor liniment, acetic turpentine liniment, and so on. Iodine may be applied as an oleate, or in combination with water and glycerin. The official liniment of iodide of potassium with soap is an excellent remedy for such conditions. Internally, quinine deservedly takes first place among remedial agents. It

may be given in does of 5 grains every three, four, or six hours, until symptoms of cinchonism shew themselves. Digitalis may be combined with quinine; and so may tincture of nux vomica, or liquor strychninæ, or liquor arsenici hydrochloricus. In convalescence iodide of potassium and bark form a suitable and often valuable combination. Free stimulation is needed in many cases—the spirits, whisky and brandy, are more reliable than wine.

Paresis after the fever requires a generous diet, the mineral acids as tonics, strychnine, and massage with galvanism or faradisation. To these remedies shower-baths and (in summer and autumn) sea-bathing may be added. Tincture of perchloride of iron is a valuable remedy in incontinence of urine.

When *convulsions* threaten or occur, the bowels should be freely moved by a dose of calomel or croton oil, the state of the bladder should be attended to, and congestion of the kidneys should be relieved by dry-cupping and poulticing, the hot-air bath, or the hot wet pack; while their action is promoted by copious draughts of water, saline diuretics, and digitalis. In urotropin we certainly possess an antiseptic and diuretic of much value. Wet-cupping has been practised with success for the relief of convulsions. Alfred Hudson, in 1837, recorded a case of recovery after two severe fits of convulsions in typhus after the abstraction of ten ounces of blood from the neck by wet-cupping and purging with calomel.

Bed-sores may be avoided by careful nursing, and by using a water-bed or a woven wire mattress. The threatened parts should be kept scrupulously clean and dry. They may be painted twice a day with a solution of one part of sheet gutta-percha in eight parts of pure chloroform, or equal parts of white of egg and rectified spirit, or equal parts of collodion and castor oil. When bed-sores have formed and are sloughing, they should be washed and dressed antiseptically. Carbolised oil (2½ per cent), or a mixture of two parts of castor oil and one of balsam of Peru, may be applied on lint as a stimulating dressing. Boric acid freely dusted over the cleansed bed-sore is an excellent antiseptic. These dressings should be covered with a layer of oiled silk or protective; or by a poultice less septic than linseed-meal, such as the yeast, carrot, chlorine, or charcoal cataplasm.

Phlegmasia dolens and *thrombosis* of the veins of the lower extremity are best treated by raising the affected limb on a gentle incline, enveloping it in wadding, and applying a long wide flannel bandage from the foot upwards. Strips of lint, smeared with equal parts of glycerin and extract of belladonna, may be laid along the hard, painful, cord-like swelling, and covered with the flannel swathe as before.

Œdema of the lower extremities generally yields to a generous diet and tonics, such as iron, quinine, and strychnine.

During convalescence from typhus the patient should be warned against assuming the upright position too soon, and against exposure to cold. The returning appetite should be controlled for the first two or

three days. After that, should the tongue be clean and the pulse quiet, a piece of boiled white fish, or chicken, or the central part of a tender mutton chop may be allowed. Costive bowels should be relieved by sipping water in mouthfuls frequently, or by enemas of cold water. Tonics may be given with advantage; but of these the most effectual are exercise in the open air, and change to the country, the seaside, or the mountains.

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INFECTIOUS CORYZA

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Definition.—By a common cold is understood the general disorder attending an acute infective catarrh of the upper respiratory passages, but especially the nasal cavities.

Etiology.—The disease may be acquired by contagion or infection from a person already suffering, that is by the transference of the infective agent from the sick to the healthy, by contact as in kissing, by infection through the air, or by fomites. It may also originate *de novo* in a susceptible person as a consequence of exposure to cold, in which case it must be assumed that the infective agent was already present in the nose or pharynx.

It is generally recognised both by the laity and by the medical profession that sudden exposure to cold under certain conditions—what is called a chill—may be followed by symptoms of very varied character. In one man it is followed by coryza, in another by bronchitis, in a third by gastro-intestinal disturbance manifested by constipation or by diarrhœa, in a fourth by rheumatic pains in joints or muscles or by lumbago, in a fifth by a bout of headache; moreover, the same individual may suffer from any one of these misfortunes at different times after exposures which appear identical. But, though the causal connexions are generally admitted, the nature of the nexus presents a difficulty even to laymen, and the prudent physician will be more disposed to admit its existence than to attempt to explain its nature.

The common expression "I have caught cold" seems at first sight to imply the idea of infection, but a little examination will prove that the verb is used in a double sense. Sometimes the speaker means to imply that he has contracted infection from another sufferer, sometimes that he has been exposed to cold under conditions which, as experience has taught him, are followed by coryza, and that he already feels the preliminary or premonitory dryness of the nasal mucous membrane.

The most efficient conditions appear to be the combination of damp clothes with cold and fatigue, as when a man who has perspired freely after exercise has to drive in an open carriage; or a golfer who has been wetted by a heavy shower is held up by a slow foursome. Coryza, gastro-intestinal disturbance, rheumatic pains, or headache may follow. A draught beating on the head is more likely to be followed by coryza. Without doubt coryza thus started *de novo* is sometimes communicable to others. A man who "starts a cold," as is said, takes it home, and gives it to his family. The suspicion therefore naturally arises that the condition which proved infectious to others is an infective, that is to say a microbic, process in the first sufferer. The common fowl is not under ordinary conditions susceptible to anthrax, but Pasteur succeeded in causing development of the disease in a cock by keeping it for a night with its feet in cold water. The ease and frequency with which the infective process is set up varies very much in different individuals and in different conditions of health; that is to say, predisposition plays a considerable part. Among predisposing causes the gouty dyscrasia, owing no doubt to the liability to catarrh by which it is accompanied, is so important that some have been betrayed into the belief that feverish cold seldom or never occurs except in gouty persons. A lax habit of body, evidenced by general want of tone and free perspiration on slight exertion, is also a disposing cause, and in children an excess of starch in the diet. There seems reason to believe that to live habitually or for many hours a day in an atmosphere unduly dry disposes to coryza; this may perhaps be accounted for by a diminution of the mucous secretion of the nasal passages, which not only has a mechanical deterrent action but also possesses some bactericidal power. Infectious coryza is particularly frequent in Great Britain during the prevalence of the cold, dry

Arctic wind, commonly known and dreaded as the east wind. Its danger is twofold, general and local; general because being not only cold but dry it promotes rapid evaporation from the skin, often moist from the effect of a bright sun, which is even hot in sheltered places, and local by drying the nasal mucous membrane and checking the secretion of mucus.

The determining cause is very frequently a sudden chilling of the surface. This is most often produced by sitting in a draught or driving in a cold wind, especially when the clothing is moist from perspiration or rain, the loss of heat due to the low temperature of the air being then greatly increased by the rapid evaporation produced by the current of air. In a predisposed person mere sitting or standing in a cold room can determine an attack. It is sometimes difficult to say whether in a particular attack the infection is acquired or autochthonous. A person who has spent an hour or two in one of the crowded, overheated, and ill-ventilated buildings in which public meetings and religious services are commonly held, often attributes the subsequent cold to chill on leaving the hot room for the cold outer air, but it is as likely to be due to infection contracted from some other member of the audience. It is estimated that in normal circumstances in the adult 73 per cent of the total loss of heat is by radiation and convection, and 10 to 20 per cent by evaporation from the skin and respiratory tract. In a crowded room the temperature of the air rises, and it is saturated, or nearly saturated, with moisture at this high temperature. The clothes, therefore, contain a large amount of moisture, derived partly from the moist air and partly from perspiration. On going into a drier atmosphere the loss of heat by evaporation from the clothes must be very great, producing a rapid chilling of the skin, which stops perspiration.

Recent investigations (5) have proved that the unpleasant sensations produced by the atmosphere of a crowded room are due not to an accumulation of carbonic dioxide nor to the malodorous exhalations of the human body, but to an excess in the temperature and the humidity of the air. The body-temperature is kept constant by the establishment of a balance between the internal production of heat and its loss by the lungs and skin; this balance is controlled by the nervous system through the vasomotor apparatus. All the energy expended in internal work is converted into heat, and at ordinary air-temperatures therefore heat must be continually eliminated. One function of the surrounding atmosphere is to carry away heat from the body, mainly by convection. An increase in the temperature and humidity of the surrounding air beyond a certain limit diminishes its power of removing heat from the body. Mere rise of air-temperature does not produce the unpleasant sensations with which every one is familiar in a crowded room or hall: the higher temperature leads to an almost instantaneous readjustment of the thermotaxic mechanism, mainly by increased perspiration and its more rapid evaporation. Experiments prove that with a given degree of relative humidity the unpleasant sensations are more readily induced the higher the

temperature of the air. It appears, then, safe to assume that in the process of catching cold, except in those cases in which the infective agent is more or less directly transferred from the sufferer to the victim, the initial disturbance is nervous: the heat-regulating mechanism is thrown out of gear, and a condition of vasomotor instability is produced. Dr. Haldane has shewn that in a hot, moist atmosphere, such as prevails in deep Cornish mines, the body-temperature rises, it may be as much as 4° or even 5° F., and that this occurs, though to a less degree, even when no work is done. On entering a cooler atmosphere the body-temperature declines gradually, but does not reach normal for an hour or more. In the warm atmosphere there is well-marked diminution of activity, both mental and muscular, and a feeling of general slackness and indifference, often accompanied, at any rate in those not habituated to the high temperature, by dyspnœa on exertion. Some of Dr. Haldane's experiments were followed by headache lasting until night. Under the conditions described there is obviously a very marked disturbance of heat-regulation, and the analogy between these conditions and those of many places of public assembly will not escape notice.

Bacteriology has not as yet done much to elucidate the etiology of infectious colds, but it seems to be proved that in different cases the same familiar symptoms may be due to the presence and development of several distinct micro-organisms. Of these the most important may possibly prove to be a Gram-negative coccus found by Kirchner in 1890 in a series of cases of the influenza type. It was afterwards found by R. Pfeiffer in enormous numbers in certain mild cases of bronchitis, and named by him *Micrococcus catarrhalis*. The same organism was found as the uniform causal agent in an epidemic in East Hertfordshire in 1905, described by Drs. Dunn and Gordon. The clinical features of the epidemic, as reported by Dr. Dunn, resembled those of influenza; while Dr. Gordon found that at the height of the attack the *Micrococcus catarrhalis* might be present in the nasal mucus in such enormous numbers that the microscopical appearance resembled an artificial culture. Dr. Cautley found in the nasal secretions of seven out of eight cases of feverish catarrh, designated influenza cold, occurring in London in 1893 after subsidence of an epidemic of influenza, a segmented bacillus belonging to the diphtheria group, since recognised by Dr. Benham in another series of cases of infectious coryza of rather severe type, and by Dr. Prosser White in seventeen out of twenty-one cases examined by him. Dr. Allen, who studied three separate severe local epidemics, isolated the *Micrococcus catarrhalis* with ease from each case examined in one epidemic, but in the other two found *Friedländer's pneumobacillus* in every case during the first twenty-four hours and sometimes later. Dr. Gordon, following out the observations of Flügge, has shewn (6) that in speaking minute particles of saliva are, as it were, sprayed into the air, and that in loud articulation this spray, carrying with it of course any bacteria present in the saliva, may be wafted to a distance as great as 40 feet by air currents, such as exist in ordinary

rooms with closed windows and no artificial ventilation. An ill-ventilated room with its hot moist atmosphere supplies therefore, if an infected speaker be present, the two conditions required to cause a healthy person to contract coryza: (1) air-conditions of temperature and moisture which tend to disturb the heat-regulating mechanism, and (2) the infective agent, in this case disseminated through the air.

Symptoms.—The early symptoms may be merely those of irritation of the nasal mucous membrane, such as are produced by mechanical or chemical irritants; that is to say, repeated sneezing followed by a copious watery discharge. In some such cases recovery ensues in a few hours or after a night's rest; they are attended by little or no constitutional disturbance, and are perhaps of the same nature as attacks of asthma; Trousseau held that they were irregular manifestations of that disorder, and occurred usually in individuals subject to it. The opinion may perhaps, without too much presumption, be hazarded that the limitation suggested is unnecessary. It must be a very common experience to go to bed with all or many of the symptoms of a commencing cold, and to wake up without them; the preliminary vasomotor disturbance which paves the way has occurred, but either because it was not sufficiently profound or because the infective agent was not present, the infective process does not develop and the rest and uniform temperature enable the heat-regulating mechanism to recover its equilibrium.

In ordinary cases of coryza the first sign is congestion of the mucous membrane, which is dry but so swollen as to block the passages, causing the well-known characteristic imperfection in the pronunciation of the nasal consonants. Smell is abolished, and taste perverted or lost. If the catarrh invade the frontal sinuses the patient complains of tense frontal headache, or heaviness in the head; and there is often, especially in children and old people, some drowsiness. Such a patient is commonly said to have a heavy cold. In other cases the inflammation extends to the antrum of Highmore, causing pain in the cheek and aching in the canine and perhaps other teeth of the upper jaw on the same side. When this complication has once been produced it is very apt to recur in subsequent attacks. The catarrhal inflammation may extend along the lacrimal passages to the conjunctivæ, so that the eyes feel hot and gritty; or the dryness of the conjunctiva may be a very early, sometimes apparently the initial, symptom (cf. hay fever). Blocking of the Eustachian tube is also a common occurrence, producing slight deafness and sometimes tinnitus. The catarrh may extend to the larynx and trachea. In some attacks the catarrhal process seems to spread by regular stages beginning in the nose, then attacking the pharynx, larynx, and even the trachea in succession; or it begins in the larynx, extending upwards in the course of a few hours, as is often observed also in true influenza. In other attacks, again, the catarrh seems to begin in the pharynx and to radiate forwards to the nose and conjunctiva, and downwards to the larynx. With this spreading type the region first attacked may have almost recovered while others are in the acute stage.

In all save the slightest cases of coryza there is some constitutional disturbance at the onset; as a rule there is a chilly feeling, sometimes actual shivering. The chilliness may be attended by pallor of the surface and so-called goose-skin. This is followed by flushing of the skin, which is dry and hot. At this stage there is usually some general malaise. In other instances the constitutional symptoms are more severe, the malaise and sense of illness are greater, there are pains in the limbs and back and some elevation of temperature. Such a patient is said to have a thorough cold, or an influenza cold. In these more severe attacks the general may precede the local symptoms, which at the onset are often slight.

After the congested condition of the mucous membrane has continued for some hours, or it may be a day or even two, a more or less copious, thin, acrid discharge is gradually established, and the onset of this stage is commonly attended by sneezing, and frequently by copious lacrimation, so that the sufferer sits alternately mopping his nose and drying his eyes. The discharge is irritating, and, favoured perhaps by the friction of the handkerchief, may produce a superficial dermatitis of the upper lip and cheek and excoriations of the nostrils. Recovery may now rapidly ensue, or the catarrh may continue for some days, the discharge becoming muco-purulent. In either case the headache and sense of fulness in the nose and head subside more or less rapidly as the discharge becomes established, but the patient commonly remains for some days in a debilitated state. One attack seems to confer no immunity, and the prolonged colds from which some people suffer appear to be due to repeated infections or relapses.

Prevention.—Isolated communities may be free for years from this disorder, which becomes epidemic after the arrival of strangers. For example, Dr. E. A. Wilson states that the crew of the *Discovery* during the recent Antarctic expedition remained, except on two occasions, entirely free from colds from the time the ship entered the ice until it reached New Zealand, two and a half years later. The exceptions, as he says, were remarkable, and may be related in his own words: "On the occasion of our unpacking a large bale of woollen clothing, long after we had been in the ice, a very virulent form of nasal catarrh ran through the whole ship's company. Undoubtedly in this case the infection was in the clothing. On the second occasion the catarrh was accounted for by the fact that our wardroom carpet was taken up for beating, and the infection, which had lain dormant for many months, was liberated, and had the usual effect." The majority of the crew were infected, and the attack on one occasion was very severe, with pronounced aching in the limbs and body and much indisposition. In civilised communities under ordinary conditions of life, especially in towns, it is practically impossible to avoid the risk of infection; but the possibility of preventing infection by isolation should be borne in mind in the case of delicate children and old persons, especially during any season when infectious colds are prevalent. An extreme proneness to coryza, as has been said, may in

children be due to an excess of starch in the diet, and in adults to a gouty tendency; in either case suitable modifications of the diet will be attended by satisfactory results. To habituate oneself to fresh air at all times and in all places is, however, the best preventive; the love of heated, ill-ventilated rooms, of heavy clothes, and generally of what is commonly called "coddling" undoubtedly disposes the victim to contract infectious colds on slight exposure; whereas open-air habits have the opposite effect, insomuch that a person sufficiently hardened may acquire the power of sitting in draughts with impunity. Proneness to catch cold may be due to the existence of local conditions, chronic rhinitis or naso-pharyngeal catarrh, adenoids or enlarged tonsils; in such cases surgical treatment greatly diminishes the predisposition.

Treatment.—The general treatment ought not to be conducted on any routine plan. No doubt it is best even for the most robust stricken by a severe "thorough" or "heavy" cold to spend a day in bed and another in the house, especially if the weather be inclement; and it is wise to take the same precaution with old people and with delicate children. But it is at least a matter for consideration whether open-air treatment is not far preferable for a patient of sound constitution suffering from a cold of no more than moderate severity: the open air by day and the open window by night. The diet should be light and simple: the old advice to feed a cold and starve a fever being certainly mistaken.

There is no line of treatment by drugs the efficacy of which is generally recognised. The views and practice of domestic authorities are as discordant as those of medical practitioners. Many popular methods rest upon the belief that if the hot, dry skin of the early stage can be made to perspire the symptoms will be alleviated, even if the attack be not cut short; with this object in view, hot draughts containing spirit of nitrous ether, sal volatile, or spirit of chloroform, or all three are given, or a dose of Dover's powder. By some it is thought that small doses of belladonna frequently repeated and combined with diffusible stimulants are useful. Others pin their faith to a dose of opium at bedtime, followed by a saline aperient in the morning. If the patient be, as is the rule, constipated, a brisk purge is indicated, and it is possible that mercury has some beneficial effect on the specific process. In gouty persons calomel is to be preferred, the dose being adjusted to their idiosyncrasies, as to which they have commonly very definite information. Salicin and the salicylates are useful in the early stage, especially perhaps in those cases in which there are aches and pains in limbs and back; salicyl-acetic acid (aspirin) has gained a certain reputation and is less depressing than sodium salicylate. Quinine or quinine salicylate may be useful in some cases. Camphor appears to have a specific though evanescent action: it is an old-fashioned remedy given internally (spiritus camphoræ x-xv ♏) with spirit of chloroform and aromatic spirit of ammonia in water; it is also used locally, and for this purpose it is recommended to sniff up from the finger a small quantity of a saturated solution in rectified spirit.

Local treatment by antiseptics has had many advocates, especially in recent years; for this purpose carbolic acid 1 in 40 (with a little glycerin), resorcin 5 grs. to ℥i. with an alkali, and formalin 1 in 40 have been recommended, sprayed well into the nostrils. Ferrier's snuff, consisting of bismuthi subnit. ʒvi., pulv. gum. acaciæ ʒii., morphinæ hydrochlor. gr. ii. to which cocaine gr. ii. is sometimes added, was formerly very much used, but has to a large extent been replaced by snuffs containing menthol with or without adrenalin, both drugs being chosen for their local astringent action.

The debility left after a bad cold may be combated by tonics, but in robust persons a change of air, as from a city to the seaside, is the most effective remedy and commonly acts with great rapidity.

Dawson Williams.

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WHOOPING-COUGH

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Synonyms.—Lat. *Pertussis infantum*; Fr. *Coqueluche*; Germ. *Keuchhusten.*

Whooping-cough, an acute and highly infectious complaint, occurs, like other zymotic diseases, in epidemics, and runs a definite course. Its special characters are severe general catarrh of the air-passages combined with laryngeal spasm and other signs of nervous disturbance. The complaint usually attacks children, and is rarely seen twice in the same individual. It is therefore uncommon to find a grown-up person suffering from it; but young and middle-aged adults, and even quite old people, may sometimes be affected. In them the symptoms are much the same as those noticed in the child, but there is a less tendency to dangerous complications.

Etiology.—Whooping-cough is undoubtedly the result of a specific virus, and many attempts have been made to determine the nature of the infecting agent. Examination of the sputum during the convulsive stage has proved the existence of various kinds of micro-organisms. Carl

Burger, of Bonn, found an elongated bacillus, isolated or in chains; and Afanassieff made cultures of a similar microbe, and injecting this into the windpipe of dogs and rabbits, succeeded in producing symptoms exactly resembling those of pertussis. Ritter examined the sputum from the bronchi and lower third of the trachea, and discovered very small diplococci, which were often arranged in straight or clustered chains. He, too, succeeded in cultivating the microbe, and could reproduce the disease with it in dogs. Unfortunately this result is not conclusive as to the real nature of the organism, for in the dog it is said that various agents will set up an apparently characteristic whooping-cough. A streptococcus which forms both long and short chains has been discovered by Cohn and Neumann; but these observers hesitate to declare it to be the specific cause of the disease. The virus, whatever it may be, seems to be thrown off from the air-passages and conveyed perhaps by the breath, certainly by the sputum. That it is highly infectious, especially in the earlier period of the illness, there can be no doubt; and facts actually observed have shewn that it can be conveyed from house to house by clothing. In all probability it is the sputum, far more than the breath, which serves as the medium by which infection is conveyed. If means be taken to disinfect the secretion from the air-passages, or to prevent it from coming into contact with healthy children, the latter, although living in the same house with the sufferer, will probably escape the disease. It has been noticed in the East London Hospital for Children that whooping-cough, when admitted accidentally into the wards, but rarely spreads to the beds around.

The susceptibility of a child to the complaint varies according to his age and physical state. Babies and the younger children take it most readily, so that it is far more common before the sixth or seventh year than at a later age. Strumous subjects are more susceptible to it than children of stronger constitution; and the state of physical depression left by certain diseases—by measles in particular—seems to prepare the child for ready infection by the whooping-cough virus. Epidemics are more common in the spring and autumn than at other seasons; and it is at these times that the greater proportion of deaths occur, for sudden changes in atmospheric conditions, by increasing the pulmonary catarrh, add to the intensity of the disease.

The period of **incubation** is not absolutely fixed; probably it varies in different individuals. In one very clear case noted by Bristowe the period was exactly a fortnight; but according to some writers it may be as short as four days. The infectiousness of the complaint begins with the earliest symptoms. It is, indeed, in this the early non-spasmodic stage that the child is most likely to be a source of danger to others; for when the whoop appears his power of communicating the disease begins to decline. Still it is not at an end until a period of at least six weeks has elapsed from the beginning of the attack.

Morbid Anatomy and Pathology.—In cases of death during an attack of pertussis the principal lesions depend upon the complication which has

determined the fatal issue. In the uncomplicated complaint we find only congestion with hypersecretion of the mucous membrane lining the trachea and bronchi; a certain amount of emphysema and collapse of lung, due to the violence of the cough and spasm, and swelling of the bronchial glands. Von Herff, from laryngoscopic observations made upon himself during an attack, found that in the early stage there were traces only of catarrh in the pharynx, larynx, and trachea; but that in the convulsive stage the catarrhal inflammation had spread to the lower surface of the epiglottis and to the mucous membrane of the arytænoid cartilages and of the cartilages of Santorini and Wrisberg. In the paroxysm the mucous membrane became dark red and covered with transparent mucus; and he always noticed a yellowish pellet of mucus, the size of a pea, on the posterior wall of the larynx. Leuriaux has isolated a bacillus from the mucous secretions in this complaint. He describes it as a short, thick, motile rod of ovoid form, Gram-positive, staining well with aniline dyes, and growing rapidly, at a temperature of 37° C., upon bouillon, agar, gelatin, etc.

The condition of the blood has been investigated by Frölich, Meunier, and others. According to these inquirers a leucocytosis is present in all the three stages of the disease. It is, however, most marked in the paroxysmal stage and shews at that time a high percentage of large lymphocytes. The leucocytosis gradually ceases as the disease declines.

The exact nature of whooping-cough is far from clear. That the disease is a general one, of which the catarrhal and nervous symptoms are the direct manifestations, can hardly be doubted. The virus affects in particular the pulmonary mucous membrane; and the peculiar spasmodic cough and whoop are usually referred to the action of the poison upon the peripheral ends of the pneumogastric nerve. But inhibition of the pneumogastric does not explain fully all the phenomena of the disease. There are, no doubt, cases in which laryngeal spasm may be due to local irritation, for in the child any violent cough, such as that set up by the entrance of food or liquid into the larynx, may be followed by a whoop; indeed, in some children it seems likely that a non-infectious spasmodic cough may be due to exceptional sensitiveness of the mucous membrane in and about the glottis: but in the real whooping-cough the nervous element is not limited to a mere laryngeal spasm. The excitability of the child, and the curious state of nervous unrest in which he remains throughout the attack, are noticeable features of the illness; and the paroxysms are marked by a general agitation, muscular as well as nervous, which is peculiar and characteristic. This general agitation may find expression in convulsive attacks which leave no ill consequences behind, or in a state allied to tetany. The vomiting, too, although sometimes perhaps a reflex act, may also be an instance of the general nervous commotion. That it is not a necessary consequence of laryngeal irritation and spasm is shewn in the case of the violent cough of enlarged bronchial glands which is not followed by retching and sickness. Moreover, in whooping-cough vomiting does not

always find its place at the end of the fit of coughing; sometimes it occurs at the beginning, and is the first sign of the coming paroxysm. This curious point seems to shew that, in such cases at any rate, vomiting is the result not of mere local irritation but of the general nervous effervescence which is so characteristic of the disease.

Symptoms.—The early symptoms are merely those of an ordinary cold in the chest; and the slight elevation of temperature (which often stands at 100° or 101° F. in the evening) is that common to the beginning of a mild catarrh. As in ordinary chills, the gastric mucous membrane may participate in the derangement, so that the patient is dull and languid, eats little, and is inclined to lie about. This state of things may go on for a few days or several weeks, the cough growing more and more troublesome, especially at night. Examination of the chest reveals nothing at first; later there may be a little dry rhonchus here and there about the back. The greater frequency of the cough at night should excite some suspicion. In the day the cough may seem of little importance; but after bed-time it is heard much more often, and is then apt to assume a convulsive character which is quite absent from it during the waking hours. It may be preceded or followed by violent sneezing and the discharge of quantities of thick mucus from the nose.

After a time the spasmodic stage begins, and puts an end at once to any uncertainty as to the nature of the child's complaint. The peculiar cough of pertussis is too well known to need description. It bursts out with boisterous violence in a quick succession of short, sharp hacks which drain the chest of air, and allow of no inspiratory relief. When the dull, reddish-purple tint of the child's face shews that the supply of air is almost exhausted, the inspiratory muscles come into play, and air is drawn into the chest with the characteristic crowing sound. The paroxysm may now be at an end for the time, but in bad cases the lungs are no sooner refilled than the cough begins again; and again the child's face swells and reddens, and grows more and more dusky until, when he seems at his last gasp, the spasm once more partially relaxes and a new supply of air is taken in. In this way all the distressing phenomena of the attack may be repeated, perhaps several times, before the child—wet with perspiration and quite worn out—sinks back with livid lips and dark swollen eyelids in his nurse's arms. If an infant, the patient sleeps heavily after the attack is over. An older child may return to his play, but often complains of headache.

At the end of the fit of coughing the patient generally vomits, and sometimes he has also an involuntary action of the bowels. The former symptom is of some moment, for, if the vomiting be frequently repeated, it may make the work of nourishing the child a very anxious and difficult one. The ejected matters consist of the food taken mixed with large quantities of thick, ropy mucus. This mucus comes in part from the lungs, but in part it comes from the stomach; for a copious flux from the stomach and bowels is a common feature of the complaint.

One peculiarity of the cough is the child's evident anxiety to stave it

off. His face all at once takes on a hard, set expression, with fixed eyes and compressed lips; then, as the desire to cough becomes more and more difficult to restrain, his cheeks grow red, his brows contract, and his forehead gets moist. Often, as the cough bursts out, there is a curious exhibition of nervous distress. The child may clutch his mother's neck as if in fear, or shiver as if with cold, or stamp with his feet upon the ground as if in a fit of rage.

During the access the pulse becomes very rapid, and sometimes can hardly be counted. Examination at the back of the chest at this time discovers nothing but wheezing sounds so long as the cough lasts, while in the long crowing inspiration all sounds are lost in the noise of the whoop. Between the attacks, if there be no pulmonary complications, the percussion note is slightly hyper-resonant, and scanty sonoro-sibilant rhonchus, with an occasional coarse bubble at the bases of the lungs, is all that can be heard with the stethoscope. In a doubtful case the marked contrast between the insignificance of the physical signs and the frequency and violence of the cough is by no means without its value in diagnosis.

In some children, who have a disposition to hernia, the strain of the cough may cause rupture; and the intense congestion which is always induced when the cough is prolonged often ends in hæmorrhage. Little cracks in the lips and gums invariably bleed, and in many cases there is hæmorrhage from the nose, the eyes, the mouth, and even the ears. Blood from the mouth comes, as a rule, from the posterior nares, very rarely from the lungs. If the paroxysms be frequent and the cough violent, the face may remain congested in the intervals between the attacks. The eyes are injected and bloodshot, the lids discoloured and swollen, and the cheeks and lips a dusky red. In these cases it is common to find signs of subcutaneous extravasation. There may be ecchymosis of the conjunctiva, and small hæmorrhages in the thickened lids; or if the strain have been unusually severe, the eyelids may be mottled purple, green, and yellow, and the sclerotics stained blood-red with the exception of a narrow white circle round the cornea.

There is one sign, occasionally present at this time, which is very characteristic of the complaint; this is a sublingual ulceration. The sore is seated at the frænum of the tongue, and may reach for a little distance on each side of the middle line. The ulcer is only seen in infants at the beginning of dentition, when no teeth but the two central incisors have been cut in the lower jaw, and is due to the scraping of these teeth against the frænum as the tongue is protruded and withdrawn during the strain of coughing. It is never seen before the beginning of the spasmodic stage.

The number of the paroxysms and the frequency of their return vary partly with the severity of the attack, and partly with the degree of judgment shewn in the management of the patient. Quiet, rest, and pastimes which amuse the child without exciting him, help to reduce the number and diminish the violence of the seizures, while emotional or

other disturbances bring on his cough and increase the worry of his nervous system. The recumbent position, too, seems to favour the return of the cough, and currents of air passing across his face, especially during sleep, are apt to excite it at once.

In different cases and, indeed, in different epidemics there is great variety in the severity of the spasms. Some children only whoop occasionally; others whoop incessantly and with violence. Young infants whoop seldom, often not at all. As a rule, the coughing fits are longer at the beginning of the spasmodic stage than towards its end; and the diminution in the violence of the cough may be noticed to coincide with an increase in the quantity and tenacity of the mucous discharge. In ordinary cases the spasmodic stage lasts about a fortnight. Towards the end of this stage the whoop only accompanies the more violent fits of coughing, and is noticed with less and less frequency until it ceases altogether. The complaint has then passed into the stage of decline, and, if ordinary prudence be shewn by the child's attendants, convalescence quickly follows. The whole time occupied by the attack varies from two weeks to eight or even ten; but the child is probably not infectious after the sixth week. In all cases where the disease is protracted beyond the normal period search must be made for adenoid growths in the nasopharynx. It is my experience that the irritation set up by these vegetations is often the cause of persistence in the cough and spasm after the whooping-cough proper is at an end.

Complications.—In the course of whooping-cough many complications may arise. Gastric disturbances and bowel complaints may give trouble, serious nervous symptoms are not uncommon, and various secondary disorders may attack the lungs and put the child's life at once into danger.

Disturbances of the stomach and bowels are the commonest of complications. The vomiting, if it be kept within due bounds, is of little importance; but if it take place with each access of cough, and this be frequently repeated, the difficulty of supplying the patient with sufficient nourishment becomes a serious one. This difficulty is increased by the copious mucous secretion which lines the walls of the stomach and interferes greatly with the digestion of the food retained. In such a state slight chills are dangerous, for diarrhœa is easily excited; indeed, a certain looseness of the bowels, with the passage of slimy stools containing much mucus and sometimes worms, is a common symptom of the disease. As a rule, intercurrent looseness of the bowels is not serious, but in hot weather a very severe watery diarrhœa may come on. This, while it lasts, may suppress all laryngeal and pulmonary symptoms, as Dr. R. J. Lee has pointed out, so that the presence of whooping-cough may not even be suspected.

In neurotic children a marked rise in temperature often accompanies the development of any gastric derangement. In uncomplicated whooping-cough the temperature is not elevated, at any rate after the first few days, so that any increase in the bodily heat may be taken as a sign of the presence of some disturbing element. This, however, is not necessarily

of a dangerous character, even if the temperature reach 104° or 105° F. Such a heat with headache and nausea, perhaps vague bodily pains and loose unhealthy motions, may often be quickly relieved by a dose of castor oil.

Nervous accidents are common. Almost invariably in the course of the disease the child is noticed to be excitable and timorous, curiously impressionable, and easily startled. In such a state the occurrence of a nervous complication is not to be wondered at. In young children under two years of age we often find exaggeration of the laryngeal spasm. At the end of the fit of coughing the expected whoop is delayed, and the child remains with open mouth, staring eyes, and haggard dusky face, making agitated movements with his arms until a partial relaxation of the glottis allows a certain amount of air to penetrate into his lungs. This complication is in any case a dangerous one; but if it be combined with inflammatory mischief within the chest the danger is great indeed. Sometimes the spasm is followed by a state of more or less complete syncope or by a passing loss of vision. Severe headache is not uncommon after a paroxysm, and, according to Troitsky, there may be temporary deafness.

The exalted nervous sensibility, especially if combined with an imperfectly oxygenated state of the blood, may be a cause of general convulsions. Convulsions occurring in the course of whooping-cough, although necessarily an alarming symptom, are not always dangerous. Cases sometimes occur in which highly neurotic children, the subjects of pertussis, are seized with convulsions, and on these passing off seem none the worse for the accident. Some of these children may be slightly rickety, but this is not always the case. There can be no doubt that in whooping-cough, as in rickets, there is a heightened nervous impressionability, and that in such a state even slight additional worries may upset the balance of the nervous system. Unfortunately these harmless seizures are the exception, and not the rule. In most cases an eclamptic attack in the course of whooping-cough announces the onset of some dangerous complication. In this way convulsions may be the earliest symptom of embolism of cerebral vessels, of cerebral hæmorrhage, of thrombosis of intracranial sinuses, of diffuse collapse of the lung, or of broncho-pneumonia.

Violent and repeated convulsions may have dangerous consequences, however trifling the cause which has set them up. During the convulsive attack the strain upon the blood-vessels, as shewn by the turgid state of the superficial veins of the face and neck, must be very severe. If this be prolonged or frequently repeated, as must happen during a series of such attacks, cerebral hæmorrhage, with more or less extensive paralysis, may ensue. Or, again, cerebral hæmorrhage, directly induced by the violence of the access of cough, may precede the convulsions and be the immediate cause of them. In most cases of the kind which have come under my notice the patient has been deeply cyanosed during the paroxysm of cough. The symptoms are those ordinarily attendant upon intracranial

hæmorrhage, and the paralysis may be permanent with wasting of muscles and rigidity of joints. In other cases complete recovery takes place, and sometimes the improvement is so rapid that it is difficult to believe that the symptoms could have been due to a blood-clot in the brain.

Many varieties of nerve-lesion may occur in the course of whooping-cough, and their pathology is often obscure. Troitsky, in an interesting paper on this subject, speaks of—(i.) Hemiplegia or a more limited paralysis ; (ii.) a form of psychical blindness; (iii.) weakness and difficulty in walking ; (iv.) transitory paralysis in all the limbs ; (v.) loss or diminution of sensibility. I have seen a temporary paresis of the muscles of deglutition in a teething baby of four months old who was nearing the end of an attack of pertussis. The child had previously had three fits not followed by ill consequences. The paroxysms of cough were not violent, and there was no twisting inwards of the thumbs or other sign of nervous worry although the child was cutting the upper incisors. The power of swallowing returned after twenty-four hours. In another case, a little girl of two years was seized with fits of maniacal fury and behaved for some weeks as if completely distraught. She lost her sight, too, for a time but this eventually returned. The patient left the hospital when the whooping-cough was at an end and was lost sight of, but on her discharge she was still subject to the maniacal attacks. The child had always been normal before this illness and there was no family neurotic history. Moebius has recorded a case of pertussis complicated by ascending paralysis in a child of three. The weakness came on towards the end of the illness, and affected first the legs ; then, as these improved, the arms ; afterwards the muscles of the neck ; and finally the diaphragm, so that respiration was conducted entirely by the abdominal and intercostal muscles. In the parts affected the reflexes were lost, but sensibility was preserved, and the electrical excitability was normal. There was no atrophy of muscle or affection of the bladder or rectum. The case ended in rapid and complete recovery, and Moebius attributed the symptoms to a multiple neuritis. Cases have also been published by Surmay, Sparks, and others, in which nervous symptoms preceding the whooping-cough were much intensified by the attack.

Aphasia sometimes occurs, and is usually combined with hemiplegia ; but Troitsky refers to one case in which there were no definite symptoms of paralysis, and to others in which these were ill-defined. The condition, in fact, might be compared to that met with sometimes at the end of enteric fever.

Although mechanical strain upon the blood-vessels is often the direct cause of cerebral lesions it is not always during the height of the paroxysms that these accidents happen. Often, indeed, they are first noticed only when the complaint is in its decline, or even nearing its close. In such cases their nature is not very clear, but similar nervous manifestations have been found after other infectious fevers, and it seems probable that they may be caused by toxins which set up inflammatory changes in the central nervous system or, as Leroux has suggested, in the

coats of the blood-vessels. According to Valentin, children between the ages of two and six years are most subject to misfortunes of this nature.

The pulmonary lesions form a very important group of complications, as it is to these accidents that death may usually be attributed. One of the most common of these is collapse of the lung. In every case where the patient is very young and the spasm violent, pulmonary collapse is to be feared, for all the conditions which favour the lesion are present at the same time. At the end of every prolonged paroxysmal cough the lungs are almost exhausted of their air, the thick mucus in the tubes offers an obstacle to their re-expansion, and the consequent state of muscular and nervous exhaustion seriously weakens the inspiratory power. A healthy infant, however, may still continue to carry on the respiratory function sufficiently, although not without effort; but if the child be the subject of rickets, reinflation of lung under such conditions and with softened ribs is often impossible. In young infants, if the pulmonary collapse be extensive, its occurrence is often indicated by a convulsive fit; or even, if the area affected be a very large one, by sudden death. In ordinary cases, where the collapsed area is of more moderate extent, the infant becomes suddenly still and cold: his face is dull white, his lips and eyelids are purple, his breathing is rapid and very shallow, and his nares act. The skin is often clammy and moist, and the internal temperature is low. The child can only be fed with difficulty, for he is unwilling or unable to swallow. He may die suddenly from syncope, or slowly from gradual extension of the collapsed area. Often the end is preceded by a convulsive fit. In children beyond infancy the effect of pulmonary collapse is less severe. The patient is stronger, and, moreover, a smaller area of lung-tissue is involved. The younger the child the greater the depression and the more pronounced the signs of deficient aeration of the blood; but at any age the complication is one to be regarded with some anxiety.

While in infants collapse of the lung is the common complication, in children of eighteen months and upwards bronchitis and catarrhal pneumonia are the chief intercurrent lesions. These, no doubt, are the consequence of a chill which causes extension of catarrh to the smaller tubes and alveoli of the lung. As long as the bronchitis is comparatively mild the whoop continues, and the symptoms generally, with the exception of a moderate rise of temperature, remain much as before. In a severe bronchitis, however, the whoop is suppressed, and all the symptoms of grave pulmonary catarrh immediately manifest themselves. If broncho-pneumonia supervene it is apt to occur in the subacute form; and, although necessarily a dangerous complication, may end favourably in a child of fairly good constitution. In the pneumonia the whoop is generally suppressed, but it may happen that laryngeal spasm, with or without a modified whoop, persists in the fits of coughing in spite of the occurrence of the complication. This, it is needless to say, adds greatly to the danger of the case.

Although catarrhal pneumonia is the common form of inflammation of the lung met with in pertussis, croupous pneumonia may occur. Its onset is often accompanied by violent and perhaps repeated convulsions; but the course of this form of pneumonia is comparatively brief, so that, although the patient may seem for a time to be in extreme danger, recovery is by no means impossible.

The pulmonary emphysema, which is almost invariably present in the upper lobes and anterior borders of the lungs, is of little moment; even if the smaller tubes participate in the dilatation. The condition is probably but a temporary one, and may be expected to subside after convalescence has been established. It may happen, however, that in an access of very violent cough an over-distended air-cell may rupture, and air be extravasated into the subpleural tissue: thence it may make its way, by the areolar tissue of the anterior mediastinum and beneath the deeper cervical fascia, to the subcutaneous tissue of the neck, the chest, the arms, the face, and even the eyelids. All these external parts are swollen, soft to the touch, and on pressure give the crepitating sensation so characteristic of surgical emphysema.

Acute parenchymatous nephritis is an occasional complication of whooping-cough, and according to Stefano Mircoli has been known to occur in no less than 12 per cent of the cases. This observer attributes the lesion to venous stasis caused by the obstruction of the vena cava through the violent paroxysms of coughing.

Sequels.—There are certain consequences of pertussis which may give trouble after the disease itself is over. A constitutional tendency previously dormant may be roused into activity. Thus, strumous children may begin to suffer from glandular enlargements and chronic discharges from which hitherto they had been free: acute generalised tuberculosis may come on—excited, perhaps, by the softening of a caseous gland together with weakened resisting power of the tissues against the invasion of the microbe; and syphilis for the first time may give signs of its presence in the system. Enlarged bronchial glands are a common consequence of an attack of whooping-cough, and chronic pulmonary diseases—such as chronic bronchitis with emphysema, asthma, chronic interstitial pneumonia, and pulmonary phthisis—not seldom owe their origin to this source.

The nervous excitability, so characteristic of pertussis, does not always subside when the disease itself comes to an end. Young children may suffer from laryngismus, the laryngeal spasm persisting and recurring irregularly without cough. In most of these cases adenoid vegetations will be found in the naso-pharynx. Older children may be left unusually timid, spiritless, and disposed to groundless alarms. They cry without reason, and are peevish and fretful at the merest trifle. Generally they are afraid of the dark, and even in daylight can hardly bear to be left alone. These signs of an unsettled nervous system may go on for months, although in other respects the child seems perfectly well. Often, however, the symptoms are kept up or even

made worse, by a gastro-intestinal derangement which I have elsewhere described under the name of "mucous disease" (15).

Pertussis is so especially a complaint of childhood that its occurrence in adult life, if not very uncommon, is always unexpected. It may, however, be met with at any age, and is invariably a tedious malady, harassing alike to the sufferer and to his medical attendant. In its main features the disease is the same whatever the age of the patient; but after the period of childhood complications are rare. There is the same violence of cough, and the nervous agitation during the paroxysm is often very evident; but the spasm is less energetic, and gives way more easily, so that the whoop is not often heard. Vomiting, too, is less common, although sometimes the patient may retch at the end of the fit of coughing. The chief complaint is of disturbed rest at night, owing to the violence and frequency of the paroxysms.

Diagnosis.—In the early period of the attack it is not easy to distinguish between pertussis and ordinary tracheitis or a pulmonary catarrh. The whoop is not a constant feature of the illness: it is not heard until the cough is fully developed, and, indeed, in many cases is never heard at all. Moreover, in the child laryngeal irritation may set up a certain amount of spasm, so that a crowing inspiration at the end of a cough must not always be taken to imply that the complaint is pertussis. Again, vomiting is not a test symptom, for it is as often absent as present. Our diagnosis must rest, therefore, upon the general characters of the cough itself, especially upon its gradual development, and not upon the presence or absence of one or two accidental phenomena. The cough at the first is mild enough, but as the days pass it gets more and more frequent and less and less easy to control. The most striking feature is its suddenness. It bursts out and cannot be restrained; and as it goes on the cheeks and eyelids grow more and more congested and red. If a child be said to cough until he is red in the face we should always think of this complaint. Again, an early sign of pertussis is the frequency of the cough at night. If a child coughs much more in the night than he does in the day, it is to pertussis that our thoughts would naturally turn. The night cough, too, is often more characteristic than that which is heard while the child is up and about. The mother should therefore be directed to notice if at night the cough be prolonged or convulsive in character, and if the child seem at all exhausted by it, or have difficulty in getting his breath. Another point, which in an uncomplicated case should open our eyes to the real nature of the complaint, is the trifling character of the physical signs. We hear that the patient's cough is incessant and distressing, and that at night his rest is continually broken by the frequent return of the paroxysms, but on examination of his chest we can find no more than a little sibilant rhonchus here and there about his back. This absence of physical signs is a very characteristic feature. In catarrhal pneumonia the cough may be violent and prolonged, but the physical signs shew the pulmonary lesion, while the history and general symptoms of the case exclude whooping-cough as its cause. So also when

the bronchial glands are enlarged the cough may be spasmodic and occur in paroxysms, but the general symptoms and signs of pressure prevent the condition being confounded with whooping-cough.

If convulsions occur it is very important to decide whether they depend upon the general nervous irritability or are symptomatic of some serious complication. In the latter case, if the complication be an attack of acute bronchitis or pneumonia the temperature becomes febrile, and the special physical signs will be discovered in the chest; at the same time the spasmodic character of the cough becomes very much modified. If collapse of the lung have occurred, the signs and symptoms proper to that lesion may be detected. So also if the complication be a cerebral one, evidence of the lesion will be quickly forthcoming. If the convulsion arise in a neurotic child from gastric disturbance acting upon a nervous system rendered by the complaint exceptionally sensitive to external impressions, or if it be due to partial asphyxia in a highly nervous subject, the eclamptic attack follows immediately upon the cough, and passes off quickly, leaving no ill consequences behind. Squinting, drowsiness or stupor left after the fit are especially ominous symptoms, as they may betoken the occurrence of thrombosis of intracranial sinuses.

Prognosis.—The mortality of whooping-cough is high, but far higher than it need be. The chief dangers of the complaint arise from the occurrence of convulsions, of bronchitis with collapse, and of catarrhal pneumonia; but with proper care in the management of the child these dangers may for the most part be avoided. It is true that if the patient be an infant with softened ribs from rickets, the danger of collapse is really great; and it may be quite out of our power to avert a fatal issue. In ordinary cases, however, judicious precautions will carry the child safely through the attack: for, as a rule, when children die in pertussis they die from a perfectly avoidable complication; and this complication too often takes the shape of an inflammatory chest affection directly induced by sending the child out of doors into the cold. As a rule, so long as the disease remains simple the prognosis is favourable; but there are certain conditions which may place the patient at a disadvantage, and these must not be overlooked when we are estimating the chances of recovery. Thus, in very young babies collapse of the lung is easily induced, and on this account pertussis during the first months of life is always to be regarded with anxiety. Again, a highly neurotic temperament is not a favourable preparation for a complaint which has a directly disturbing influence upon the nervous system; and these cases, too, demand especial care in their management. The course of whooping-cough is also affected by the presence of adenoid growths in the naso-pharynx. The irritation set up by these vegetations may be sufficient greatly to increase the intensity of the spasm, and probably also to maintain the nervous element in the cough for weeks together. Most of the cases of protracted whooping-cough, or of apparent relapse after recovery, are met with in children who are troubled with these vegetations.

The occurrence of any complication adds much to the gravity of the

case. Great agitation and excitement on the approach of the access of cough, or extreme cyanosis during its course, make us fear the onset of convulsions. Should an eclamptic attack occur, we scan very narrowly the condition in which the patient is left when the fit is at an end. If he seem contented and cheerful there is so far no cause for anxiety; but if he be drowsy and stupid, or shew any special sign of cerebral lesion, or if he lie pale and still with active nares and quick shallow breathing from collapse of lung, death is almost certain. Convulsions which usher in a pneumonic complication, even although repeated and violent, are rarely immediately fatal, and if the lung inflammation be of moderate extent, the case may still end favourably. Laryngismus stridulus, with extensive bronchopneumonia or serious bronchitis in a rickety subject, must excite our gravest apprehensions. With regard to the likelihood of recovery from the paralytic consequences of the complaint, Charles Leroux has found that the older the patient when attacked the better his chances become. Infants, if they do not die, are apt to retain some degree of permanent paralysis, but in later childhood the prospects of the patient improve with his years. Still, the prognosis is always serious for, according to Valentin, taking all ages together, only 40 per cent of the cases make a complete recovery.

Treatment.—In order to guide a case of whooping-cough to a favourable issue we must do our best, while promoting the healthy nutrition of the patient, to ward off the complications to which the chief mortality of the disease is due. We must remember that the mucous membranes are already in a state of catarrh, and therefore highly susceptible to changes of temperature, and that to send the patient daily out of doors, with little regard to the state of the weather (as is so often done), is hardly the way to keep his chest free from grave intercurrent disease.

The best way to shorten the attack and prevent the onset of complications is to confine the patient strictly to two rooms, and to keep him both by day and night in a properly medicated atmosphere. The temperature of the rooms should be maintained as nearly as possible at 65° F.; and if the rooms do not communicate, the child must be carried from one to the other wrapped from head to foot in a blanket. The air can be medicated in various ways. Creosote or eucalyptus oil may be volatilised from a metal saucer placed over a spirit lamp; a solution of carbolic acid (one part in thirty of water) may be vaporised by means of Dr. R. J. Lee's "steam draft inhaler"; or sulphurous acid may be diffused through the room by burning small sulphur pastilles at short intervals. In children who are old enough to follow directions other topical remedies may be used in addition. Thus a 2 per cent solution of salicylic acid or resorcin may be sprayed for one minute into the child's throat every two or three hours while he inspires deeply. The spray is far more useful than the brush for applying remedies in this complaint. The latter usually excites the utmost alarm and annoyance; indeed, the mere sight of it is enough with most children to bring on a paroxysm at once.

While the fever lasts the patient should be kept in bed: afterwards

he may be allowed to dress, but must still remain in the medicated atmosphere, at any rate until the spasmodic stage has come to an end. When he leaves a room the windows and doors should at once be thrown open so that the fresh air can enter freely until the time comes to warm and medicate the room again for the child's return. By this means the disease is treated topically, while complications—at any rate such as arise from chill—are guarded against. To diminish still further the risk of cold it is well for a time to forbid a bath, or, indeed, any washing of the child's body; for few children with whooping-cough can be submitted without danger to the exposure involved in an ordinary nursery bath. The dress should be warm, especially over the chest, and it is advisable to keep this part covered with a layer of cotton-wool. The child must be amused with unexciting games, and it is better not to tease him with lessons, at any rate until convalescence is well advanced. In regulating his diet, foods which promote fermentation and acidity, such as potatoes, farinaceous puddings, jams, and fruit, are better avoided. These things make the child flatulent and uneasy, disturb his rest at night, and increase the fluster of his nerves.

In addition to the topical treatment, internal remedies should be given to allay nervous irritation and reduce spasm. The drug upon which above all others I am wont to rely is the butyl-chloral hydrate given in doses of one grain every two, three, four, or six hours, according to the age of the child. It may be usefully combined with double the quantity of bromide of potassium. Another favourite remedy is the sulphate of zinc in doses of one-sixth of a grain (for a child twelve months old) given with half a drop of liq. atropinæ sulphatis (B.P.) twice a day for three days; then every six hours for three days longer; afterwards with increasing frequency until slight dilatation of the pupil is noticed. It is advisable to keep the pupil thus dilated for at least a week. Antipyrin is preferred by some practitioners; it is given, in doses of one grain for every year of the child's life, every four, six, or eight hours. All these remedies have a very decided influence in reducing the spasm and shortening the attack, and will be found quite sufficient by most practical men. Many others may, however, be given; indeed, the whole list of anti-spasmodics and sedatives is open to the prescriber if he wish for variety. This class of remedy is to be resorted to directly the complaint is recognised as whooping-cough, and is of especial value at an early period of the illness. As we approach the end of the spasmodic stage there are two other drugs which have great value if the spasm be slow to yield. These are quinine in full doses, and the liquid extract of grindelia. Of the former one grain may be given, with one of antipyrin, twice a day to a child of one year old, and one grain of each may be added for every year of the child's life, until a dose of five grains is reached. The quantity of the grindelia extract to be given to an infant is fifteen drops every four hours. Either of these will usually make an immediate impression upon the complaint. At the same time it must be remembered that obstinate cases are mostly met with in children who are

troubled with naso-pharyngeal vegetations. Search, therefore, should be made for adenoid growths, so that, if present, they may be removed without unnecessary delay. Counter-irritation of the chest is usually advised, and is greatly relied upon as a domestic remedy. It is no doubt of service if pulmonary catarrh be well marked, or there be a tendency to collapse of lung.

Any complication which may occur should receive early attention. Excessive vomiting may be controlled by small doses of cocaine (one-sixth of a grain twice a day to a child of one year old). It may be remarked here that in bad cases, when vomiting is frequent and distressing, advantage should always be taken of the temporary lull which follows the fit of retching to administer food. At this time nourishment is urgently required; the stomach is freer of mucus, and a longer time is available for digestion before the next bout of coughing sets in. If the bowels be loose, a dose of castor oil will usually set them right. Excess of spasm or unwonted nervous excitement may often be checked by chloral and the bromides; and immediate relaxation of the glottis usually follows the dipping the child's hands into cold water. Convulsions and the pulmonary complications must receive early treatment, and any temporary weakness or tendency to syncope must be combated by free stimulation. During convalescence a change to a dry bracing air is of great advantage in calming nervous excitement and restoring strength.

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MUMPS

By Eustace Smith, M.D., F.R.C.P.

Synonyms.—Lat. *Cynanche parotidæa, Parotitis epidemica*; Fr. *Les oreillons*; Germ. *Ziegenpeter.*

Mumps, or contagious parotitis, is one of the milder specific fevers, and occurs for the most part in epidemics. It is most common in children between the ages of four and fourteen, but is seen, although less often, in older persons. The disorder is a highly contagious one; but although a cause of considerable temporary discomfort, is rarely dangerous to life. Still, as consequences of a more or less serious nature may arise from it, it is unwise to treat even slight cases with indifference.

The incubation-period, according to the report of the Clinical Society (14), may vary from fourteen days to twenty-five; but Dr. Parker Douglas has reported a case in which the disorder only declared itself on the twenty-ninth day after the last exposure. When the complaint begins it is infectious from the very first, and can be communicated while the patient is merely ailing, and before any signs of glandular swelling are to be detected. Its duration is ten days to a fortnight, but the patient must be considered unsafe to others for at least a week longer.

Morbid Anatomy and Pathology.—The inflammation attacks the salivary glands, and is believed to spread from the duct to the substance of the gland. It causes infiltration into the cellular tissue around, but rarely ends in suppuration: when the complaint is at an end the gland is left uninjured. In the orchitis, however, which is apt to occur in mumps, the testicle may afterwards atrophy. In these cases the inter-canalicular tissue is little altered, but there is a parenchymatous as opposed to an interstitial sclerosis. The tubules are alone affected, and shew marked hypertrophy of their basement membrane, with atrophy of their epithelial lining and disappearance of their lumen.

Mumps is probably due to a microbe. Pasteur found in the blood rod-shaped bacteria, but failed to reproduce the disease with them; and Bordas describes a micro-organism which, he states, is developed in large numbers in the blood as early as eight hours after the beginning of the illness.

Symptoms.—The local affection may be the earliest sign of ill-health, but this is uncommon. As a rule there are premonitory symptoms, and the complaint begins with fever, often accompanied in the child with headache and vomiting. The patient looks and feels ill, and the temperature rises to 102° or 103° F. Mirchamp has observed a symptom at this time which he states is peculiar to infectious parotitis. If a sapid substance, such as vinegar, be brought into contact with the mucous membrane of the tongue, a painful reflex secretion of saliva occurs in the gland

about to be affected. He states that this symptom is present even in cases in which the infection first shews itself in the testicle or is limited to it. In a few hours stiffness is complained of in the jaw, and there is aching and tenderness on one side in the hollow beneath the ear. This part is soon noticed to be full, so that the depression disappears; and as the swelling spreads forwards and backwards from this point it comes to involve the greater part of the side of the face and neck. The skin over it may be pale or have a pinkish tint, and the part is tense, elastic, and very tender. Dr. F. Tresilian has noticed that at an early period of the complaint the opening of Stenson's duct of the parotid becomes distinctly visible. This duct, it may be remembered, opens on the inner surface of the cheek on a level with the second upper molar tooth. In health it is often difficult to detect, but in mumps it can be seen at once as a small bright red projection on the mucous membrane. It remains visible until the inflammation of the gland subsides. The inflammation may remain limited to the parotid first attacked; but usually it spreads to the other side of the face, to the salivary glands beneath the jaw, and sometimes to the fauces and tonsils. The face is then curiously widened, and the prominence of the chin is lost in the swelling of the neck. The disease takes three or four days to reach its height, for, as a rule, the glands are involved one after another. When fully developed there is no change for a day or two; then the swelling begins to subside, and by the tenth or twelfth day all fulness has disappeared. The length of the attack depends upon the quickness with which the glands successively take on the morbid action. It is rare to find the inflammation at its height at the same time on both sides of the face. Often after the subsidence of the swelling on the one side a distinct pause occurs before the other side begins to suffer; and it may happen that the latter becomes affected only after an interval of weeks, as if from a true relapse.

All through the earlier period of the illness, and until the swelling begins to decline, the aching of the jaw continues and is increased by movement; so that mastication is painful, and even the acts of speaking and swallowing add to the patient's discomfort. On this account saliva tends to collect in the mouth, but there is no increase in the salivary flow; indeed, as the swelling subsides, secretion for the time may be suppressed [Jaccoud], leaving a troublesome dryness of the mucous membrane. Sometimes the temperature declines on the second or third day, but it generally remains high until the complaint is fully developed, and then falls more or less abruptly to the normal level.

The above is the ordinary course of an attack of mumps; but the symptoms may be much less striking. Often, especially in sporadic cases, the swelling is insignificant, with little feeling of illness; or, with much swelling and local discomfort, the temperature is normal, and the general health hardly disturbed; or, again, the constitutional symptoms are severe, with little swelling or pain in movement.

Complications.—A remarkable feature of the complaint consists in the so-called metastases which sometimes occur, chiefly in adult patients.

These secondary lesions are inflammatory in their nature, and should be regarded rather as further manifestations of the virus than as true metastases. The most common of these complications, in the male subject, is orchitis; in the female the breasts inflame, or there is œdema of the external genitals, or perhaps swelling and tenderness of the ovaries and enlargement of the inguinal glands. In exceptional cases orchitis may occur as an early symptom before any swelling is noticed elsewhere; or may be itself the only sign of the complaint, without inflammation occurring in the parotid or other salivary glands. Usually it comes on towards the end of the attack; or even after all signs of swelling have disappeared from the face. With the pain of the inflamed organ there is usually a rise of temperature and a return of the feeling of illness, but sometimes the only complaint is of local discomfort. If an interval of apparent health have followed the subsidence of the parotid swelling, the appearance of the complication may be preceded or accompanied by more serious signs of general disturbance. There may be high fever and delirium, or obstinate vomiting and purging, or alarming symptoms of prostration.

The orchitis lasts from three to five days, and is sometimes followed by very rapid atrophy of the testicle. Many instances of this untoward sequel to the inflammation are recorded by French writers. Thus, Lereboullet refers to the case of a young soldier of twenty-two in whom orchitis began on the fifth day of the mumps. The inflammation soon subsided, but was followed by such rapid wasting that in three weeks the affected gland was reduced to the size of a haricot bean.

The above is not the only form of metastasis met with. Sometimes the orchitis is followed quickly by signs of inflammation of the membranes of the brain. This complication is a rare one, but many cases are on record. Although serious enough in appearance, it can be treated with considerable hopes of success. Thus, Dr. G. H. Dowdney has recorded the case of a man aged thirty-five who, during an attack of mumps, exposed himself to chill by driving ten miles in an open trap. This took place on the fourth or fifth day of his illness. On the next day (the fifth or sixth) orchitis began; and the first signs of meningitis were noted on the day following. The man was seriously ill for some weeks, but eventually recovered. A very similar case in a boy of fifteen is narrated by Dr. Monro. Here also the meningitis was preceded by orchitis, and although in the end recovery was complete, the boy was left for a time with unsteady gait, difficult articulation, and marked agraphia. From these latter symptoms it would seem that the inflammation is not always limited to the cerebral coverings. Lannois and Lemoine have described a case in which aphasia and localised paralysis of one arm followed such an attack and lasted five days. In another case aphasia combined with right hemiplegia persisted for several months. They suggested that to produce such consequences the attack must have consisted really of a meningo-encephalitis, the inflammation having spread from the membranes to the substance of the brain.

The nervous sequels in mumps are not confined to cases which begin with such violent symptoms. As in other forms of acute specific disease, nervous derangements of more obscure mechanism may be met with. Thus, Joffroy has reported a case of generalised paralysis with loss of deep reflexes, but without cerebral symptoms, which he attributed to peripheral neuritis; and Jalon, one of optic neuritis with subsequent atrophy of the optic nerve. Dr. R. Percy Smith, too, has known acute mania to follow an attack of mumps; and Campani has reported a case in which night-blindness was a noticeable symptom.

A temporary facial paralysis is sometimes met with: this seems to be due to direct extension of the inflammation to the sheath of the facial nerve, although it may happen in cases where there has been little parotid swelling and but slight local discomfort. In a case kindly communicated to me by Mr. A. Maude, the local symptoms of mumps were mild, but the general symptoms were of exceptional severity. The facial paralysis was first noticed in the third week, and lasted nearly a month; there was no deafness or otorrhœa.

Other complications are sometimes met with which may vary according to the prevailing type of the disorder. Thus, in one epidemic cases of gastro-intestinal derangement are noticed with abdominal pains; in another epistaxis is common; in a third there are occasional cases of endocarditis [Jaccoud]. Albuminuria, with or without bloody urine, has also been noted. Still, with regard to this matter of complications, it may be repeated that as a rule the course of the complaint is simple and mild, and that secondary disorders are rare if common prudence be exercised in the management of the case.

Perhaps one of the least unfamiliar consequences of mumps is deafness of one ear. This infirmity may come on in the course of the complaint or later. It occurs in two forms. In the first, the inflammation spreads through the Eustachian tube to the middle ear. In this case the hearing is usually restored by treatment. In the second, the deafness begins suddenly at an early period of the illness owing, it is thought, to an inflammatory process set up in the labyrinth or cochlea, or both. The middle ear is unaffected. The attack of deafness may be accompanied by noises in the head and sometimes by pain. If the labyrinth be the seat of the lesion there is also vertigo with nausea and vomiting. In this form treatment can do little, and the deafness is generally permanent. As it is usually confined to one side, and may give rise to no pain, the damage to the organ is often discovered only by accident.

Diagnosis.—Mumps is a primary complaint, and is therefore easily distinguished from the non-specific parotitis (parotid bubo), which is always a secondary disease, and occurs as a complication of many forms of acute illness. Symptomatic parotitis (as it is called) may attack both sides of the face, but, unlike mumps, it may end in suppuration.

In a very mild attack of mumps, if orchitis occur, there is danger of the primary disorder being overlooked through the prominence assumed by the complication. Therefore, in an epidemic of mumps a case of

orchitis should always suggest a careful inquiry and examination of the face. But even if no swelling or tenderness be noticed in the salivary glands and they entirely escape the infection, the orchitis may still be due to mumps. In such a case the diagnosis depends upon the existence of an epidemic, the sudden onset of the illness, and the lapse of several days between the beginning of the general symptoms and the occurrence of the orchitis. Mirchamp's symptom might be a help in these doubtful cases (*vide* p. 586).

Treatment.—However mild the attack may be, quiet and rest should be strictly enjoined, as the complications and unpleasant consequences of the disorder are due mainly to imprudences committed during its course. On this account they mostly occur in the milder cases, where the general symptoms are trifling, and with little local discomfort.

The patient should be confined to his bed while the fever lasts, and when the temperature falls should still keep the house until all local symptoms have subsided. The food should consist of strong soups, meat jellies, pounded meats, milk, eggs beaten up, and the like—such things as need no mastication. If necessary the liver must be relieved by a mercurial purge; or, if there be a foul tongue and much gastric derangement, an aperient draught of rhubarb and heavy carbonate of magnesia may be given, flavoured with cardamoms, spirit of chloroform, and peppermint water. For local treatment hot bread-poultices should be applied, and frequently renewed; or the part may be anointed with a salve composed of one part of guaiacol in twenty parts of mixed vaseline and lanoline, as recommended by Ragazzi, and covered with a layer of cotton-wool. It is well to cleanse the mouth and throat with an antiseptic gargle several times in the day. A very grateful application for this purpose is made by dissolving salol to saturation in an ounce of rectified spirit with forty drops of chloroform. Thirty to forty drops of this solution added to a tumbler of warm water make a wash pleasant to use and strongly antiseptic.

Of the complications—orchitis is to be treated by warmth, and mechanical support, and the earlier hot poultices are applied to the inflamed part the better the chance of reducing the intensity of the inflammation and relieving the discomfort. In all children of twelve years and upwards it is advisable, as Dr. Dukes has suggested, to watch the temperature, for increase in the bodily heat may possibly signify the onset of the complication. If meningitis occur, leeches to the temples followed by ice to the head and by aperients must be resorted to. The alarming constitutional symptoms sometimes noticed before the onset of the complication generally cease when the latter shews itself. If there be great prostration, stimulants must be used and warmth applied to the extremities.

EUSTACE SMITH.

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E. S.

GLANDULAR FEVER

(DRÜSENFIEBER)

By DAWSON WILLIAMS, M.D., F.R.C.P.

GLANDULAR FEVER may be defined, provisionally, as an acute infectious fever, characterised by inflammatory swelling of the deep cervical and other lymphatic glands, and by constipation; and followed by a considerable degree of anæmia and depression.

Pathology.—E. Pfeiffer described the disease in 1889, and expressed the opinion that it was an acute specific fever previously unrecognised. He pointed out that it occurred in narrowly limited epidemics, but that most of the children of a family in which one member suffered contracted the disease. This observation has been confirmed by later writers; and Park West states that, in an epidemic affecting an isolated community in Ohio, ninety-six cases occurred among the children of forty-three families; only about twenty children between the ages of seven months and thirteen years escaped. From the occasional occurrence of nephritis as a complication, Hesse has drawn an argument in favour of the contention that the disease is specific, as Pfeiffer maintained. The onset of the disease is acute, and the adenitis one of the earliest symptoms; while pharyngitis, though it may occur as a complication, is seldom severe. Park West observed only four cases of severe pharyngitis in ninety-six cases; and usually there is no pharyngitis at all. That the disease is not an aberrant form of mumps is shewn by the facts that parotitis has not been known to occur; and that in the Ohio epidemic it was ascertained that fifty-seven of the ninety-six children had had mumps before the glandular fever, or soon after it. The suggestion that the cases are examples of German measles, or some other exanthematous fever without the exanthem, is not tenable in view of the fact that intermediate cases with rash have never been observed, and that in the extensive Ohio epidemic no

rash was observed in any of the cases. The adenitis runs a fairly regular course, reaching its maximum in from two to four days, and then subsiding gradually, while at the same time groups of glands other than those first affected may be enlarging. The glands shew little tendency to suppurate; indeed it is very doubtful whether this accident ever happens.[1] Bacteriology has not as yet thrown any light on the pathology of the disease, but no thorough examination has been made. The obstinate constipation characteristic of it, coupled with the frequency of enlargement of the mesenteric glands, led v. Starck to suggest that the general symptoms and the adenitis were due to infection derived from the intestines, or were produced by the absorption of toxins from the retained fæces. The place of the disease in nosology would appear to be near non-venereal or so called climatic bubo (*vide* vol. on Tropical Diseases).

Course.—The incubation-period is probably about seven days, with extremes of five and ten days. The onset is sudden; complaint is made of pain in the neck, which is held stiffly, of pain on swallowing, and sometimes of pain in the abdomen. The face is flushed, there is tenderness in the anterior triangle, the temperature is 101°-103° F., the tongue is furred, there is anorexia, sometimes vomiting, rapid pulse, and the ordinary symptoms of pyrexia. Examination of the throat reveals no condition sufficient to account for the stiffness of the neck and dysphagia, nor for the pyrexia. The mucous membrane may be healthy, or a little reddened; or there may, of course, be chronic granular pharyngitis or tonsillitis, which affections are extremely common in children. On the second or third day of fever an elongated swelling, uniform to the eye but on palpation found to be due to three or four enlarged glands, is perceived beneath and towards the front of the sterno-mastoid muscle. In nearly all cases the adenitis is first perceptible on the left side; it reaches its maximum in from two to four days, and then begins to subside. A little before the swelling on the left side reaches its height the corresponding glands on the right side begin to swell, and they run through a similar course. Other groups of glands, the posterior cervical, the axillary, the inguinal, may likewise become enlarged and tender. Abdominal pain and tenderness and enlargement of the liver are present in most cases; enlargement of the spleen and of the mesenteric glands occurs in many, probably in more than half. Constipation is obstinate except in the very mildest cases, in which it may be replaced by frequent small mucous stools. In some severe cases the beginning of convalescence is marked by the passage of a large amount of green mucoid material from the bowel. The temperature usually attains its maximum (104° F.) about the third day, and remains high so long as groups of glands continue to enlarge. The pulse may continue rapid for a day or two after defervescence, which usually takes place during the second week. Complications

[1] Comby's opinion to the contrary appears to rest on Neumann's observation of the presence of staphylococci in certain cases; but Neumann himself held that the cases he was dealing with were not examples of Pfeiffer's Drüsenfieber.

are rare, the most important being nephritis, which may be attended by hæmaturia; but the disease usually runs a benign course, though occasionally, as Moussous has pointed out, the general symptoms are so severe as to suggest typhoid fever. Convalescence is apt to be prolonged, the child being left in a condition of general depression with anæmia, from which complete recovery does not as a rule take place in less than a couple of months. The enlarged glands subside gradually, and have disappeared before the general health is completely restored.

Age.—The disease is one which affects children; it is not uncommon in infancy, but must be very rare after puberty; though Drs. Donkin and Coutts have mentioned instances in which young adults were affected during a family epidemic.

Treatment has little or no effect on the course of the disease. The pain in the neck and swollen glands may be relieved by a cold compress, or by belladonna fomentations, but these measures do not prevent the development of adenitis on the opposite side. Constipation can be relieved by a full dose of calomel; but the condition returns at once, and Park West saw reason to believe that this treatment was followed by greater depression and a more prolonged convalescence. Small doses of calomel (gr. $\frac{1}{10}$ to $\frac{1}{12}$) are probably of use in regulating the bowels and preventing decomposition in the intestinal canal. During the fever the child should be kept in bed or on the couch, and should have simple liquid nourishment. During convalescence the patient should be guarded from over-fatigue or exposure to cold, and should receive as much nourishing food as he can digest. Cod-liver oil and iron preparations, or the syrup of the phosphate of iron, are indicated; and as soon as the enlargement of the glands has disappeared change of air may be advised.

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D. W.

RHEUMATIC FEVER

By Sir W. S. Church, Bart., K.C.B., M.D., F.R.C.P.
The Pathological Section by W. Bulloch, M.D.

Synonyms.—Acute or Subacute Rheumatism.

Acute Rheumatism, or Rheumatic Fever, is a disease more easily described than defined. No line of separation can be drawn between the cases classified as subacute and acute; and in this article rheumatic fever will be considered as equivalent to a synovitis accompanied by pyrexia, and generally multiple.

Under the name rheumatism is included a vast medley of pathological conditions having little or no connexion with each other, except in the presence of pain in the muscles or about the joints. The word, at first explanatory of the pathology of the morbid condition (the pain being attributed to rheum[1] flowing down from the brain and settling in the affected part), has now become a convenient term to embrace myalgic, neuritic, and arthritic pain dependent on very various causes of whose nature we are often ignorant.[2] The inclusion of three very distinct affections—gout, osteo-arthritis, and gonorrhœal arthritis—under the head of acute rheumatism vitiates to a great extent all the statistics of the disease given by the older writers.

Sydenham separated acute rheumatism from gout (76), giving an excellent clinical description of the disease, and remarking that "it is commonest in autumn, chiefly attacking the young and vigorous"; he goes on to say that it very rarely kills the patient. The mortality during an acute attack is very small, and of those who die in the course of the attack, death, excepting in cases of hyperpyrexia, is almost invariably due to secondary lesions, such as peri-, myo-, or endocarditis or, more rarely, pneumonia or pleurisy. I say almost invariably, for in very rare instances death occurs suddenly without hyperpyrexia or any discoverable injury to the lungs or heart. One such case I have seen myself. A girl aged nineteen, a nursemaid, was taken ill on May 25, 1870, with pain in the right foot, followed by pain in the legs and hands; the joints were swollen and very painful. She was admitted to St. Bartholomew's Hospital on June 1st. She was fairly well nourished; besides pain in

[1] Jejuna, vigila, caleas dape, tuque labora,
Inspira calidum, modicum bibe, comprime flatum,
Haec bene tu serva si vis depellere rheuma.
Si fluat ad pectus dicatur rheuma catarrhus:
Si ad fauces, bronchus; si ad nares, esto coryza.
Schola Salernitana, cap. lxxxii.

[2] Ballonius is credited with being the first to use the word rheumatismal in its present sense. *De rheumatismo et pleuritide*, 1642.

her limbs she complained of some discomfort at the epigastrium; her tongue was coated, appetite gone, bowels costive; there was some vomiting; the urine was high-coloured, alkaline, free from albumin; skin moist; left knee much swollen. States that she has had very little sleep; pulse 108, good volume, heart-sounds natural, respiration normal, temperature 99·5° F. During the afternoon of the day of admission she was very restless, and complained of increasing pain at the epigastrium and in the præcordial region. At 9.30 P.M. she suddenly became very pale, sick, and pulseless, with pupils widely dilated, and died at 10.15 P.M.[1] Nothing abnormal was found in any organ except very slight beading along the margin of the mitral valve. Senator[2] speaks of sudden death occurring in "paroxysms of palpitation and oppression" not dependent on cardiac complications.

Mortality and Prevalence.—Rheumatic fever is a ubiquitous disease, and is met with in all parts of the world, in the arctic as well as the torrid zones, but is more frequent in subtropical and temperate climes. No race is exempt, although Europeans in the tropical and warmer temperate regions appear to suffer from it more frequently than the native races.

The mortality directly attributed to rheumatic fever in the reports of the Registrars-General for Great Britain and Ireland is no measure of the frequency of its prevalence or of the sufferings produced by it; a very large proportion of the deaths returned as due to valvular disease of the heart and endocarditis (not infective) being due to antecedent rheumatic fever. The number of deaths ascribed to it in England during the year 1903 was 2382, being 4·62 in every thousand deaths, in Scotland the proportion was 3·78, and in Ireland 2·75 per 1000 of deaths. This mortality varies very little from that which is found in other parts of the world (*vide* Appendix I.). In England, according to the Registrar-General's returns, the death-rate from rheumatic fever and rheumatism of the heart has been steadily falling for the last twenty years, in 1884 the annual death-rate from it being 101 in every million persons living, which number had fallen in 1904 to 70. How far this diminution in mortality is due to lesser prevalence of the disease, to better treatment, or to changes in the mode of registration it is impossible to determine, for it is to be noted that the deaths attributed to valvular disease and endocarditis (not infective) have increased in far larger proportions; 231 deaths per million of persons being attributed to this cause in 1884, whilst in 1904 the number has risen to 430.

Etiology and Geographical Distribution of Rheumatic Fever.—The similarity which acute rheumatism bears in many of its features to gout has led to *the humoral or chemical hypothesis* of its production; a conception

[1] See also a somewhat similar case of Dr. Goodhart's (42).

[2] Senator refers also to Rathery's case (62), but on turning to his reference I find it was a case of a girl aged three, who was seized with dyspnœa and became cyanosed, and died ten hours later. The autopsy shewed pleurisy and collapse of lung and ante-mortem clot in the right ventricle.

formerly supported by many observers in this country, who considered that a morbid poison was generated in the body as the result of altered or imperfect metabolism, and gave rise to the disease. Prout is said by Fuller to have been the first to throw out the suggestion that it is due to lactic acid; and this view, further amplified by Todd, was accepted by Fuller as the most probable of all the hypotheses up to that time propounded. The experiments of Richardson were discredited by the more extended ones of Rayher; and the observations of Sir W. Foster (30) and of Külz on the occurrence of articular pain and swelling in diabetics under treatment by lactic acid have not been confirmed by later experience. Dr. P. W. Latham in his Croonian Lectures considered the exciting cause of rheumatism to be the presence of lactic acid together with uric acid, the latter acting as an irritant to the nervous centres and to the subsidiary ganglia in connexion with them; and Dr. Haig suggests that any cause producing pyrexia may determine the precipitation of uric acid in the joints, and thus give rise to the arthritic symptoms. It is difficult to believe that uric acid can give rise in our bodies to such very different pathological conditions as those met with in gout and acute rheumatism: the similarity is superficial whilst the whole pathological and clinical course is different. If the evidence in favour of the chemical hypothesis of acute rheumatism be unsatisfactory, the same may be said of the nervous hypothesis first suggested by J. K. Mitchell seventy years ago, and advocated by Canstatt, Day, and others; for neither the nutritional lesions which occur in and about the articulations in connexion with spinal degenerative changes, nor those which follow injury to or division of the nerves supplying the joints, resemble the conditions met with in acute rheumatism (8).

It is now very generally admitted that rheumatic fever belongs to the class of acute infective diseases, although opinions still differ with regard to the specific organism by which it is produced. In the Milroy Lectures of 1895 Dr. Newsholme brought forward a large amount of statistical evidence to support the opinion that acute rheumatism is one of the infectious diseases. He shewed that the rates of the mortality and of the frequency of the disease fluctuate in a manner very similar to those of such infectious diseases as scarlatina and erysipelas (*vide* also Longstaff, 55, 56).

The charts constructed by Dr. Garrod from the statistics of Lange in Copenhagen and Gabbett in London, shewing the curves during a series of years yielded by first attacks of rheumatic fever, afford no satisfactory evidence that they are influenced by atmospheric or climatic causes. Still more recent investigations by Dr. T. Thompson and Mr. Major Greenwood, junior, into the monthly record of the rainfall at Greenwich and the monthly admissions of rheumatic fever into the London Hospital also shew no evidence of any direct connexion between the rainfall and the prevalence of the disease, while Dr. Newsholme, who considers rheumatic fever as "essentially a soil disease, due to a saprophytic soil organism," is of opinion that it is "drowned out in wet years, multiplies rapidly in dry years, and is

transferred to the human recipient by unknown means." Hirsch, from the absence of any constant meteorological influences and the remarkable fluctuations in the prevalence of the disease at the several points which have been carefully watched, considers that "rheumatic fever now seems to have an assured place among the acute infective diseases."

Very interesting observations made on the frequency with which rheumatic fever occurs in *particular houses*, tend to support the infectious hypothesis of the disease. Friedlander [1] of Leipzig saw twelve cases from the same house in three years; and during another three years met with eighteen cases from two houses. Edlefsen, at Kiel, reports that of 728 cases of rheumatic fever occurring in 492 houses, he met with

2 cases in one house	100 times.	5 cases in one house	5 times.
3 ,, ,,	27 ,,	6 ,, ,,	1 time.
4 ,, ,,	5 ,,	7 ,, ,,	1 time.

Drs. Fiessinger, Mantle, and Dalton have also recorded the occurrence of groups of cases arising within short periods in the same house (cf. p. 606).

It has generally been held that cold and damp situations are contributory factors in the prevalence of rheumatic fever; but more recent investigations tend to shew that meteorological conditions have little or no influence on its prevalence.

The British Army, consisting of young men at a time of life prone to the disease, and placed under similar conditions as to hygiene, food, and work under very various climatic conditions, affords excellent material for the investigation of the effect of climate on the incidence of the disease. An examination of Appendix II., which I have abstracted from the Army Medical Reports, shews that it is impossible to associate the number of attacks with any peculiarities of climate. Malta prior to 1894 gives a high ratio, whereas for 1903 the number is very low. The figures also shew how small is the direct mortality from the disease; in 1903 only one death is recorded out of 116 cases among the troops in Great Britain and Ireland, and 5 in foreign stations. That *racial differences* have some bearing on the question is shewn by the fact that whilst the average number of attacks per thousand among our British troops in India is larger than amongst the same troops when quartered in Scotland and Ireland, the ratio given by our Native Indian Army is the lowest of all.

The statistical tables of the Army Medical Department do not separate rheumatic fever and rheumatism of the heart from rheumatism; but by the kindness of the Director-General I was able to obtain information on this point for a considerable number of years prior to 1894, and they agree fairly closely with those in the Report for 1904 (*vide* Appendix II.).

That *chill* is probably a most important factor in determining an attack of rheumatic fever is not only borne out by general experience,

[1] Quoted by Dr. Newsholme in the Milroy Lectures, 1895.

but to a certain extent by the geographical distribution of the disease. Contrary to what is usually believed, high and dry lands, where the temperature varies between wide limits in the twenty-four hours, appear to be particularly conducive to rheumatic fever. Thus we find it of comparatively frequent occurrence in Egypt, the Cape, Central Arabia, and the high elevated plateaus of Bavaria and Mexico (48); whilst in lower and moister localities, of a more even but equally high temperature, it is infrequent. The military statistics are in accordance with this statement, the average number of attacks per 1000 of strength being higher in Egypt, South Africa, and the Mediterranean stations than in Scotland or Ireland. Unfortunately the military returns during the Crimean war do not afford data for comparing the proportion of cases of rheumatic fever with those of rheumatism. Our troops in the Crimean war were exposed to damp and great cold as well as fatigue. The only information I find bearing on this point is the statement by Dr. Lyons: "Rheumatic pericarditis seems to have been very rare during our army's occupation in the Crimea, notwithstanding the rigour of the climate."

The influence of fatigue and exposure in a dry and otherwise salubrious climate is shewn very prominently by the military returns during the Egyptian and Cape wars.[1] In Egypt, during the years that our troops were on active service in the field, the average number of admissions for rheumatic fever reached the high ratio of 29·68 per 1000 men; and in the Cape during the years of the Kaffir war an increase of over 5 per cent in the cases of rheumatic fever was seen.

The United Kingdom, and England in particular, is regarded by many writers, especially on the Continent, as pre-eminently the country of acute rheumatism. It is almost impossible to form any opinion as to the frequency of its occurrence in the United Kingdom. I have arranged in the Appendices IV. and V. the returns that I have obtained from the metropolitan and provincial hospitals. The returns from the provincial hospitals are very imperfect, and of less value than I had hoped—whether as indicating the proportion rheumatic fever bears to other diseases, or as shewing the effect of position, climate, nature of the soil, or character of the population on the occurrence of the disease. They are roughly in accordance with the Registrar-General's returns, which shew that the death-rate per million living is lower in the Eastern and North-Midland divisions of England than in the others; the highest death-rates being in the North-Western division and in London and Wales.

The population of our large manufacturing centres appears to suffer more than that of our rural districts; but this may be due to the larger proportion of cases in country districts treated in their own homes. The returns from the East Coast are lower than those from the West; but with the exception of Newcastle there are no returns from large towns, such as Hull and Hartlepool. The prevalence of the disease in the Isle of Man and Whitehaven is remarkable.

[1] The military returns during the war in South Africa in 1899-1902 were not available at the time this article was written.

Scotland suffers less than England, corroborating the evidence given by the military returns; and there is no proof that the disease is less frequent, as has been stated, in Cornwall,[1] Guernsey, and the Isle of Wight than in many other parts of the United Kingdom of equal size. Senator quotes London as having the highest percentage of any European city; and gives its average as 11·5 per cent of the sum total of disease. This average very greatly exceeds that now found in the statistics of the London hospitals; and I find that an examination of the cases treated in the clinics of the physicians of the Charité Hospital, Berlin, during the years 1889-94 give very much the same percentage of cases of rheumatic fever (4·87) as those yielded by the medical statistics of St. Bartholomew's Hospital. Rheumatic fever, as Hirsch has remarked, is "ubiquitous, and is more evenly spread over the world than is ordinarily stated."

Influence of Seasons (38).—That seasonal changes play some part in the prevalence of rheumatic fever is undoubted. All the collected statistics shew fluctuations in the curves of its frequency during the various months of the year, which appear fairly constant in the localities where the statistics are compiled, but present great discrepancies when compared with those drawn up in other places. Dr. Newsholme attributes the prevalence of rheumatic fever at different times to the influence of ground-water. He considers that low ground-water is an indication of certain conditions of dryness and temperature of the subsoil favourable to the growth of a telluric contagium for rheumatic fever; whilst admitting that low ground-water unassociated with the other necessary conditions may not be productive of rheumatic fever, he contends that we never find excess or prevalence of rheumatic fever with a high level of ground-water. Somewhat similar conclusions have been arrived at by Dr. L. Weber. In London the old and widespread belief that the disease is most common in the autumn appears well founded.

Dr. Gabbett tabulated 2000 cases of rheumatic fever, admitted to the London Hospital during the nine years 1873-81, according to the months; and I have arranged his figures in the form of a chart for comparison with that drawn up by Dr. L. C. P. Phillips of 1998 cases at St. Bartholomew's Hospital during the twelve years 1882-93.

It will be seen that in each series the curve made by the numbers of first attacks is identical with that made by the whole number of patients. It will also be noted that the curves made by Dr. Gabbett's figures are almost identical with those at St. Bartholomew's Hospital during a period subsequent to the nine years tabulated by Dr. Gabbett; the only difference is that at the London Hospital the maximum is reached in November, whereas in Dr. Phillips' chart the maximum is found in October: this difference is probably due to the London Hospital chart

[1] I find that in the ten years 1882-91, 235 deaths in Cornwall are ascribed to rheumatic fever and rheumatism of the heart, and the Registrar-General gives a death-rate of 47 per million living for the county in 1903. A correspondent who practises at Redruth says: "Cases of acute rheumatism are not infrequent in my own practice."

dealing with the admissions, whilst that of St. Bartholomew's deals with the onset of the symptoms.

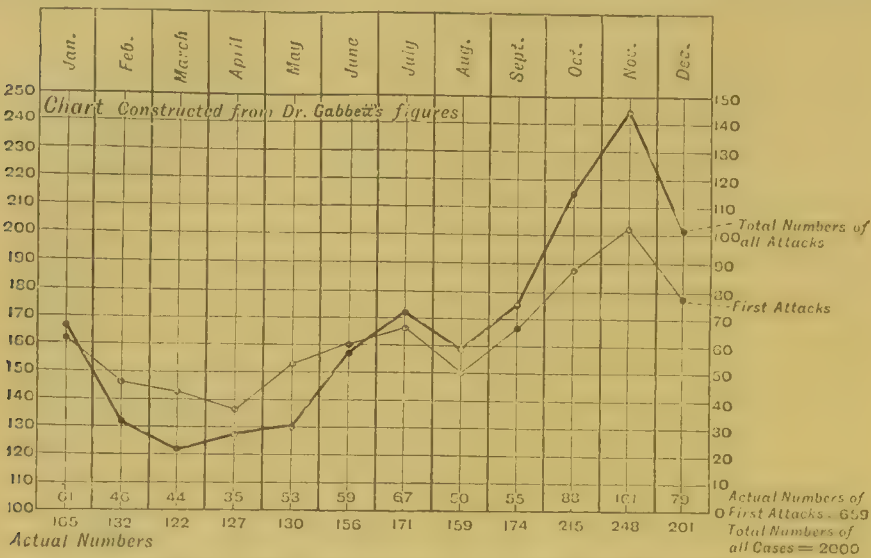

CHART 8.—Cases of rheumatic fever in the London Hospital, 1873-81.

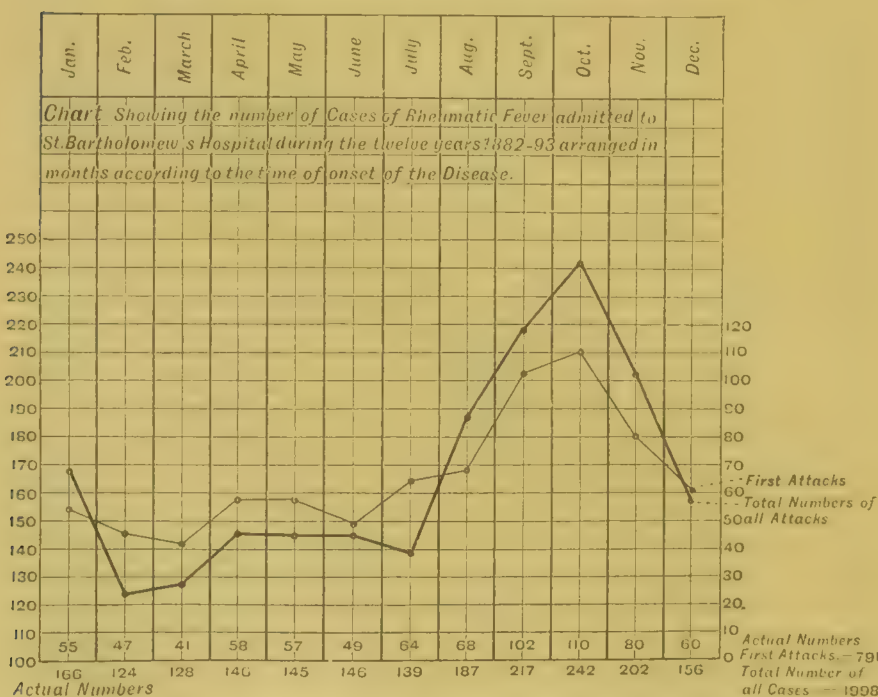

CHART 9.—Cases of rheumatic fever in St. Bartholomew's Hospital, 1882-93.

The curves of the second series of cases treated in St. Bartholomew's Hospital agree very closely with the former charts in general features.

The curve of first attacks corresponds almost exactly to that of second or subsequent attacks, as is the case in the earlier charts; the maximum number of cases is met with earlier in the year, in August instead of October, and the fall does not take place so suddenly, the numbers remaining almost stationary for August, September, and October.

Dr. T. Thompson and Mr. Major Greenwood, jun., have tabulated the admissions for rheumatic fever to the London Hospital since 1873. Their figures therefore include Dr. Gabbett's given in Chart 8, as well as those of more recent years. Although the chart is constructed on a somewhat different principle from Dr. Gabbett's and my own, the curve

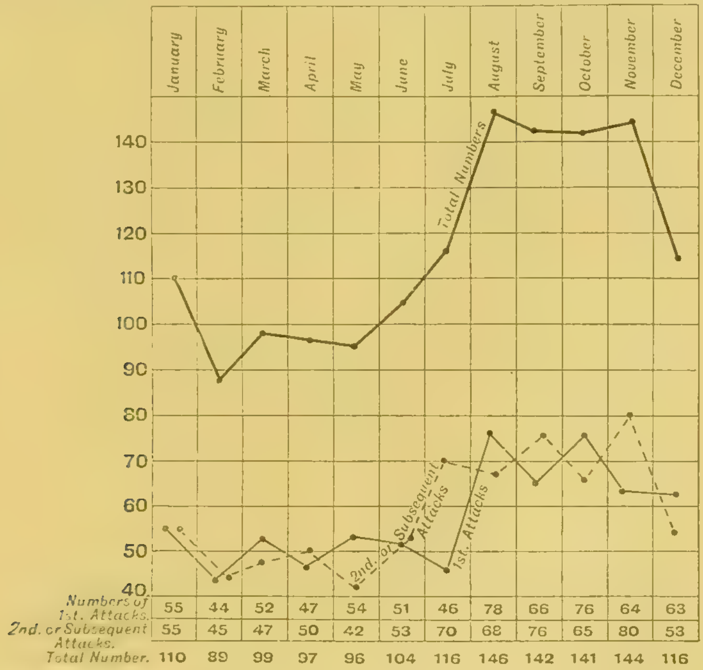

CHART 10.—Second series of cases of rheumatic fever in St. Bartholomew's Hospital, 1894-1904 inclusive, and half of 1905.

of the seasonal incidence of rheumatic fever is substantially the same as that given by Dr. Gabbett, and presents much the same features as that formed by the cases at St. Bartholomew's Hospital.

The constancy of these seasonal variations lends probability to the infective hypothesis of rheumatic fever, and supports the view that its immediate cause is a micro-organism capable of multiplication in a suitable nidus outside our bodies.

Sex (38).—It is generally stated that acute rheumatism is more prevalent in men than in women, because of their greater liability to exposure in the course of their work. This explanation of the greater frequency of the disease in men, if it exists, cannot be maintained. In London, if not elsewhere, the disease is as common, if not commoner, among indoor workers as among those following outdoor employments;

and the figures given above shew that it is most prevalent at a season of the year when the weather is not usually severe, and is least prevalent during February, March, and April, the three months in which outdoor workers here are exposed to great vicissitudes of temperature and weather. The relative frequency of the disease in the sexes is extremely difficult to ascertain; the statistics of various localities and of different writers differ very widely. At St. Bartholomew's, and at most of the

CHART 11.—Mean daily averages of admissions for rheumatic fever to the London Hospital 1873-1903 inclusive. (Thompson and Major Greenwood, jun.)

other metropolitan hospitals whose figures I have gone through, the numbers of the two sexes are nearly the same, the excess being slightly on the side of the men, which is in agreement with the mortality returns of the Registrar-General over a series of years; and it must be remembered that in most hospitals the medical beds for men exceed in number those for women. Women are particularly liable to the disease after parturition and prolonged lactation, especially if the recovery from childbirth has been imperfect and attended with uterine discharge; but the numbers given in the older statistics must be received with caution, as many cases of puerperal septicæmia or pyæmia are included, and a

considerable fraction of the alleged acute rheumatic attacks are not true rheumatic fever, but the acute stage of chronic osteo-arthritis. (*Vide* also p. 646.)

Occupation according to my experience has little or no influence on the incidence of rheumatic fever. The very elaborate analysis of 326 cases of the late Dr. Sibson (72), appears to me to shew only that those occupations which contain the largest number of young subjects yield a higher proportionate number than others. Female domestic servants formed one-third of Sibson's whole series, and nearly three-fifths of his series of female cases; a class which mainly consists of girls and women at the time of life most disposed to the disease. Among the male patients, 158 in number, 82 followed laborious outdoor employments and 76 either worked mainly indoors or were without known employment.

Age.—In considering the influence of age on the disease first attacks only should be regarded; for the tendency of rheumatic patients to frequent attacks at short intervals falsifies any deductions which can be made from the general statistics of the disease. Acute rheumatism is essentially a disease of adolescence and early man- and womanhood. Of 943 instances of first attacks of which I have records—

135	occurred under 10 years of age	= 13·99	per cent.
412	between 10 and 20 ,,	= 43·58	,,
244	,, 20 ,, 30 ,,	= 25·66	,,
128	,, 30 ,, 40 ,,	= 13·57	,,
23	over 40 years of age	= 2·43	,,
1	age not known.		
943			

These figures shew the greater liability of youth and early adult life. Still no period of life is exempt; the disease has been described in a baby of twenty-three days, and in another of four weeks (71); and a first attack from which a perfect recovery was made is reported in a man over eighty (16).

Heredity.—That some families are predisposed to the disease is probable from the frequency with which we see several children in the same family affected sooner or later by it. Dr. Cheadle is of opinion that the tendency to rheumatism is transmitted as strongly as the tendency to gout; and that hereditary predisposition is found in 70 per cent of rheumatic children. Dr. L. Weber uses the recurrence of rheumatic fever in several members of the same family as an argument in favour of its being "a house disease, the underground of houses in certain localities being infiltrated with the virus, which will be set free after prolonged dryness." The occurrence of rheumatic fever in phthisical subjects is not very uncommon. I have met with families in whom there appeared to be a very strong proclivity to tuberculous disease and rheumatic fever; and with one in which nearly all the children suffered either from rheumatic fever or tuberculous disease of the lungs. I have also known

several instances of pulmonary tuberculosis, beginning shortly after an attack of rheumatic fever[1] associated with severe valvular mischief, in which I had no doubt that the tuberculous disease was really subsequent to the attack of rheumatism. Statistics of heredity, with reference to an ill-defined disease, easily confounded with gout and rheumatism, appear to me to have little value, and those drawn up from hospital patients to be quite worthless;[2] that the predisposition to the disease is hereditary in the same way as gout or insanity seems to me to require further evidence.

W. S. C.

Morbid Anatomy.—Opportunities for examining the bodies of those who have died in the earlier stages of rheumatic fever are rare. In most cases death has ensued after more than one attack and there is, especially in regard to the heart, a combination of old and recent lesions. The changes in the *joints* are not as a rule striking. There may be an increase in the quantity of synovial fluid, which is serous or turbid with a varying number of cells. The hyperæmia which no doubt existed during life has mostly disappeared, although a swollen and infiltrated condition of the synovial membrane may persist. According to Cornil and Ranvier the cartilage is always more or less affected, and shews enlargement and multiplication of its cells. In the majority of cases such changes have been found to be focal rather than diffuse. Occasionally the cartilage may be affected throughout its entire thickness. The sheaths of tendons also shew changes similar to those met with in the joints.

When heart complications have ensued very definite appearances are produced. These may be found in the pericardium, the endocardium, or the myocardium. In rheumatic *pericarditis* there is an increase of fluid in the pericardial sac; sometimes serous, frequently turbid, it may also be tinged with blood. The wall of the pericardium is usually roughened and in a state of inflammation which varies very much in degree up to the most severe cases of adhesive pericarditis, ending in total obliteration of the pericardial sac.

Endocarditis.—Although the changes are most frequently seen and most severe in the valves, the membrane lining the cavities of both auricles and ventricles may be affected. Rheumatic endocarditis has been frequently described, but a want of unanimity prevails in regard to the interpretation put upon the changes. For a long time it has been customary to separate verrucose from malignant endocarditis. In the majority of cases the rheumatic virus produces the verrucose type, although in recent years Litten, Drs. Poynton and Paine, and others have described cases of malignant rheumatic endocarditis. Ziegler regarded the verrucose rheumatic endocarditis as mainly a thrombotic process, an

[1] Dr. J. A. Austen published four cases of rheumatic fever followed by lung disease, but it is not clear that in his cases the tuberculous disease of the lung was not in existence before the rheumatism.

[2] For the relative frequency of rheumatic fever in the families of rheumatic and other patients, *vide* (38).

opinion shared by Romberg, Weichselbaum, and Harbitz. Achalme described the process as occurring in three stages, viz. œdema, proliferation, and cicatrisation. The only careful investigation of rheumatic endocarditis in recent years is that published by Königer, and on his results, with which my own observations on three acute cases closely agree, the following description is based. It will be remembered that the endocardium consists of several layers, one of the most important being that immediately underneath the endothelium and known as the subendothelial layer. It is composed of a soft ground-substance containing very few fine fibrillæ and some large cells. Underneath this is the elastic part proper, which in some places is clearly divisible into two layers, the deeper one of which is in contact with some connective tissue (sub-endocardial layer) which seems to connect the endocardium with the connective tissue of the cardiac muscle. The valves are composed of a fibrous plate, derived from the *annulus fibrosus*, and are covered with endocardium. In the normal adult the endocardium proper is devoid of blood-vessels.

As far as can be made out, the earliest changes of rheumatic endocarditis shew the presence of a homogeneous fibrin-like substance in the subendothelial membrane; with fibrin-stains this mass does not take the characteristic colour and appears to be more of the nature of a coagulation-necrosis with swelling and homogeneous transformation of the ground-substance. In the earliest lesions the endocardium is not perceptibly elevated. In older lesions a prominence ensues, the endothelial cells necrose, and a deposit of platelets and fibrin takes place from the circulating blood, as occurs in ordinary thrombosis. Proliferation of the fixed cells of the endocardium occurs at variable times—often early—and by the time that the vegetation is well formed there are signs of organisation, which is followed by the formation of granulation-tissue and ultimately by cicatrisation. In autopsies of cases of acute rheumatism there is often evidence of pre-existing endocarditis to which a fresh inflammation has been superadded. Königer has attempted, on histological grounds, to separate rheumatic endocarditis from other verrucose processes in the lining membrane of the heart. He considers the characteristics of the rheumatic inflammation to be (1) widespread distribution of the lesions, which are, however, focal; (2) that the lesions are relatively deep-seated; (3) the intense reactive phenomena; and (4) the œdematous condition of the endocardium.

The *myocardium* is probably often affected, but it is only in severe cases that the changes are pronounced. These consist of cellular infiltrations of the intermuscular connective tissue, especially in the region of the atrio-ventricular boundary, and also in the connective tissue accompanying the blood-vessels. These cell-infiltrations are usually focal and are prone to become homogeneous towards the centre. The presence of hyaline thrombi in the small arteries has also been noted (Romberg).

In recent years the histology of the *rheumatic nodule* has been investigated, especially by Drs. Poynton and Still. I have examined four

nodules, two excised in an early stage during life and two removed after death. In the centre there is a homogeneous substance arranged in layers and containing in its periphery some cells. Drs. Poynton and Still have described the hyaline-like substance as fibrin, but with fibrin-stains (Weigert's, Kockel's) I have not obtained characteristic reactions. The process seems more allied to coagulation-necrosis, with a homogeneous transformation of the fibres of the connective tissue of the cutis in which the nodule lies. The histological limits of the nodule are not sharp, but gradually pass into a cellular reactive area in which tortuous vessels are usually very marked features (*vide* also p. 655).

Lungs and Pleuræ.—The pleural cavities often contain an excess of fluid, sometimes serous, sometimes fibrinous. Suppurative exudates are mostly the result of mixed or secondary infections. In the few cases of pneumonia which have been examined after death the lesion has been lobular in character. A genuine lobar pneumonia due to pneumococcus has also been observed.

The sequels of rheumatic endocarditis may occur in the form of bland *infarcts* of the spleen and kidney. When high fever has existed for some time cloudy swelling of the parenchymatous cells of the great abdominal organs has also been frequently noted.

The changes in the *nervous system* in rheumatic chorea have not been satisfactorily worked out. From their recent work Drs. Poynton and Paine (94) consider that there are numerous small lesions external to the blood-capillaries and caused by the *Diplococcus rheumaticus*, "which is driven by the blood-stream into these positions."

Bacteriology.—Of the numerous hypotheses put forward at different times to explain the occurrence of rheumatic fever the one most commonly held in recent years attributes the disease to some form of infection. The basis of this belief is, on the one hand, the clinical and pathological characters of the disease, and especially the occurrence of fever, polyarthritis, angina, endocarditis, and pericarditis; on the other hand there is, as was first pointed out by Hirsch, the fact that remarkable fluctuations occur at various localities, so that at one time the disease becomes infrequent while at another it assumes epidemic proportions. The data which have been held to prove the epidemic occurrence of rheumatic fever are often, however, vague and unconvincing, and this applies especially to so-called local and "house" epidemics, a considerable number of which have been recorded (Chomel, Lebert, Edlefsen, Fiessinger, Lange, Fiedler). Small "family" epidemics have been reported by Thoresen, Mantle, Meyer, Talamon, Turner, Hawthorne, Josseran. Since the individuals affected have been, in many cases, blood-relations, the alleged hereditary disposition to acute rheumatism deprives observations of this kind of a good deal of their value as evidence of infectivity. Nurses and sick-room attendants—not blood-relations—are not known to be infected from patients suffering from rheumatic fever (Pribram). Of the greatest rarity and difficult to interpret are cases of simultaneous affection of mothers and newly-born children. In Schaefer's case a

woman aged thirty-five was attacked with severe polyarthritis of rheumatic character. Four days later she bore a child which on the third day shewed swelling of various joints. In spite of treatment by salicylates the disease was protracted in both cases. Pocock treated for rheumatic fever a female eight months pregnant. During the attack a child was born, and within twelve hours it was seized with arthritis, sweating, and high fever. Mother and child made a rapid recovery under salicylates, the mother with a cardiac lesion, the child without complication. In searching for the cause or causes of acute rheumatism we are met at the outset by the considerable difficulty that, while the concept of the disease is clinical, all modern scientific inquiry shews how unsafe it is to rely solely on such a basis. Although most physicians who have studied rheumatic fever regard it as a disease *sui generis*, this belief is not universal. Assuming that it is an entity we expect it to be caused by a specific virus, as bacteriological research has taught us (1) that each infection is caused by a definite infective agent, (2) the given infection is produced only by the infectious agent, (3) the given infectious agent always produces the given infection and no other.

Before dealing in detail with the bacteriology of acute rheumatism, it must be admitted that the problem reduces itself to this:—Is rheumatic fever a specific disease? If so, we are justified in expecting a specific virus as its cause. If we find preponderating evidence of ordinary infectious microbes, it may be that rheumatic fever is not a disease *sui generis*. In such a case we should not be justified in saying that it cannot be an entity, as these ordinary microbes might be found in practically every case and still not be the cause of the disease, but merely of secondary importance.

A large number of investigations have been carried out in the case of rheumatic fever, and search for the hypothetical virus has been made in parts where there is reason to believe that it exists, thus in the joints, blood, heart lesions, nervous system, lymphatic apparatus of the throat, and in the urine. From analysis of the results obtained by the investigation of these tissues and fluids it is manifest that most divergent conclusions have been reached. This is due partly to the difficulty of the certain diagnosis of rheumatic fever, and to inefficient precautions in the bacteriological investigations, and partly to the interpretation put upon the observed facts. From consideration of the published work as a whole it is remarkable how discordant the results obtained are in a disease which appears to be so well defined from the clinical point of view. Relatively few of these researches were conducted with the stringent details of diagnosis, technique, and results that have characterised the working out of many well-known infections, and herein lies the chief difficulty in discussing and interpreting the results hitherto obtained.

(*a*) *Examination of Joint Lesions.*—Bacteriological examination of the joints during life or after death has shewn either that the cultures remain sterile or that growths of cocci occur alone or in association with microbes which are manifestly contaminations. Kraus found a streptococcus in

the joints of children suffering from acute synovitis. Guttmann, in a case regarded as rheumatic fever but evidently septic (multiple abscesses in kidneys, muscles, pericardium), found *Staphylococcus pyogenes aureus.* Mantle grew on gelatin two organisms—a coccus and a sporing bacillus. G. Lion and Buday both found streptococci in joints examined post-mortem. Sahli, who had uniformly negative results up till 1892, isolated *Staphylococcus pyogenes citreus* from a case of rheumatic fever. The examination took place fourteen hours after death, and the coccus was found in the synovial membrane but not in the joint fluid. Maragliano found streptococci and staphylococci. Melkich found a sporing anaerobic bacillus known as the Bacillus of Achalme (*vide* p. 613) in four cases in the periarticular fluid. In three other cases a similar bacillus was found in association with pyogenetic cocci. Menzer, in an examination of five cases during life, found two sterile. In the remaining three (one of which was complicated with gonorrhœa) he obtained cocci which were practically without pathogenetic effect on rabbits; in the gonorrhœal case the cocci producing swelling of the joints after intravenous inoculation in the rabbit. Drs. Beaton and Ainley Walker found the so-called *Micrococcus rheumaticus* (*vide* p. 613) in one case *intra vitam* in the joint fluid, and Dr. Beattie found it in three cases after death.

In comparison with these positive results a number of writers have failed to find micro-organisms in the joints or have occasionally obtained contaminating microbes. Thus Chvostek in 17 cases had negative results only, and the same has been the experience of Michaelis (12 cases), Philipp (6 cases), Cole, and Pribram. In one fatal case examined a few hours after death Pribram was unable to obtain any cultivations. Chvostek has also pointed out that growths may be obtained from the joints of animals after death, even when no inoculations had been made. Apparently in no case examined in the early stage of the joint affection has any organism been found during life. In many of the positive cases the disease had existed some time, or the examination was made a number of hours after death.

(*b*) *Examination of the blood and of the heart lesions before and after death* have also given discordant results. In a large number of cases the cultures have remained sterile. In a certain number, especially of post-mortem examinations, various microbes have been found either singly or in combinations. Of the older observations it is sufficient to mention the following. In 16 cases Mantle found a coccus associated with a bacillus on gelatin cultures. Lion described a coccus, but was unable to cultivate it. Sahli obtained growths of *Staphylococcus citreus* in one case. Both during life and after death Achalme found a large sporing anaerobic bacillus, a result confirmed by Papillon, Thiroloix (5 cases), Triboulet and Coyon (1 case), Bettencourt, Carriere, Melkich (21 times in 26 cases), Lucatello. In 6 out of 10 cases Oppenheim obtained a Gram-staining coccus. Opposed to these are the negative results obtained by Michaelis, Gerhardt, Jez, Kühnau (67 cases), Chvostek, Sittmann, Triboulet and Coyon (4 cases), de St. Germain.

The more modern researches on the bacteriological examination of *the blood* during life in acute rheumatism have mostly yielded negative results, such as those of Cole (1904), Lewis and Longcope (1904), Thue (1902), Menzer (1902), Philipp (1903) (21 cases), T. M'Crae (1903), Bulloch and Thompson (1906) (14 cases), Lenhartz (1903).

In the post-mortem examination of cases of rheumatic fever with *endocarditic and pericarditic lesions* the number of positive results increases. Of the older researches the most important are the following:—Klebs (1878) found "monadina" in 18 cases of *rheumatic endocarditis*. Birch-Hirschfeld in 5 cases found staphylococci; Sahli, *S. citreus*. In 5 severe cases of rheumatic endocarditis, von Leyden (1894) found cocci in 4, in only one of which, however, he was able to isolate the microbe on ascitic fluid. Inoculation of the culture into the rabbit produced fever and in one case death; post-mortem, the coccus could not be recovered. Triboulet and Coyon in a case of endo-pericarditis found Achalme's bacillus and a diplococcus. Apert (1898) also obtained Triboulet's coccus *intra vitam*. Thiercelin found a similar coccus 48 hours after death. In 1899 an important observation was made by Westphal, Wassermann, and Malkoff. In a girl, aged 19, dead from endocarditis and nephritis associated with chorea, Wassermann found a streptococcus in the blood, brain, and valves. It grew best on alkaline media, and in a series of 80 rabbits the inoculation of the culture produced joint affections after an incubation-period of 9-10 days. The microbe was recoverable from the joints after death. Drs. Poynton and Paine (160) in 1900 obtained in 8 cases of acute rheumatism a diplococcus which grew in chains in liquid media. The organism grew best on a mixture of milk and bouillon acidulated with lactic acid. In 3 cases it was isolated in pure culture during life in cases of acute pericarditis. It was also found in pericardial fluid after death as well as from the cardiac valves and throat. Later (1905) they reported having found the diplococcus altogether in 32 cases in various rheumatic lesions, including the rheumatic nodule. Drs. Beaton and Walker confirmed the results of Drs. Poynton and Paine in 15 cases, including 8 of acute rheumatism, 3 of chorea, 4 of acute endocarditis in rheumatic subjects. The exact source of their cultures may be seen in the following table of their cases:—

Case.	Source of Culture.
1. Acute rheumatism with peri-endocarditis .	Heart-blood, post-mortem
2. Acute rheumatism	Knee-joint, *intra vitam*
3. Acute rheumatism with endocarditis . .	Heart-blood, post-mortem
4. Subacute rheumatism + mitral stenosis .	Urine
5. Acute rheumatism	,,
6. Acute rheumatism with nodules . .	Blood, *intra vitam*
7. Acute rheumatism	Blood from ear lobule, urine
8. Subacute rheumatism, adherent pericardium	Heart-blood, post-mortem
9. Chorea, heart-failure . . .	,, ,, ,,
10. Chorea	Urine
11. Chorea, heart-failure . . .	Heart-blood, post-mortem

Case.	Source of Culture.
12. Fungating endocarditis	Heart-blood, post-mortem
13. " "	" "
14. Acute endocarditis	Blood from ear lobule
15. " "	" " "

In most cases the coccus was pure ; in the post-mortem isolations it was occasionally contaminated with *B. coli.* In two out of three cases in which it was isolated from the lobule of the ear it was contaminated with *Staphylococcus albus.* Lewis and Longcope (1904) isolated (12 hours after death) a similar coccus from the median basilic vein of a case of chorea dying with endocarditis. Negative results have been obtained by Weichselbaum, Harbitz, Schottmüller, Bulloch and Thompson. Harbitz examined 6 cases of characteristic rheumatic endocarditis and could find no microbes microscopically or on culture. Dr. Thompson and I examined the endocarditic lesions in 4 cases of severe rapidly fatal rheumatic fever and found no microbe microscopically or on cultivation.

In *Rheumatic Pericarditis* the results have been equally divergent, the following organisms having been found: *Staphylococcus citreus* (Sahli), Achalme's bacillus (Achalme), *Staphylococcus aureus* (Triboulet), Achalme's bacillus and diplococci (Triboulet and Coyon), diplococci (Poynton and Paine, Beaton and Walker). In 3 cases examined with Dr. Thompson, I found the pericardial fluid, taken shortly after death, to be sterile. In one unusually severe case in a boy aged 15 with a history of repeated sore throat, and one previous attack of rheumatic fever, there had been high fever, generalised nodules, severe peri- and endocarditis. The examination of the pericardial fluid, pericardial membrane, endocardial vegetations, rheumatic nodules yielded sterile cultures, although different media were inoculated and maintained aerobically and anaerobically. The microscopic examination of the pericardium, endocardium, and nodules failed to shew any microbes.

(*c*) *Examination of Pleurisy and Pleuritic Exudates.*—Positive bacteriological results have occurred in a very few cases; the organisms found being streptococci (Gilbert and Lion), *Staphylococcus aureus* (Goldscheider), B. of Achalme (Thiroloix). In by far the greater number of cases the exudates have been found sterile (Kracht, A. Fränkel, E. Levy, Fiedler, Aschoff, Singer, Pribram, de St. Germain, Bulloch and Thompson).

Pneumonia, which is a rare complication of rheumatic fever, has seldom been the subject of investigation. In one fatal case (autopsy by Chiari) Pribram found the pneumococcus.

(*d*) *Examination of Angina Rheumatica.*—The lesions in the lymphatic apparatus of the throat in cases of acute rheumatism have been the subject of repeated investigation. The bacteriological examination of this region is beset with difficulties, especially in regard to the interpretation of the results obtained. Further, it is likely that the importance of throat examinations in cases of acute rheumatism has been overestimated, when it is remembered that the frequency of such lesions is subject to

great variations (1·7-80 per cent) (Pribram). The principal bacteriological examinations of the rheumatic throat have been carried out by F. Meyer and by Menzer (Berlin) with divergent results. Meyer took some of the exudate from the tonsils and inoculated it directly into bouillon, and employed the mixed culture thus obtained for inoculation into rabbits. In about a week after inoculation he observed arthritic lesions from which he obtained diplococci, staining faintly by Gram's method. The exudate in the joints was opaque, of mucoid consistence, and contained a number of leucocytes. The joint lesions were constant, and in about 10 per cent of the animals inoculated the serous membranes were affected with serous or sero-sanguinolent exudates, which were for the most part sterile. In 25 per cent of the cases endocarditis verrucosa or ulcerosa was also induced, the cocci being found in pure culture in the lesions. The blood and other organs were, however, sterile. The cocci were obtained as above in 12 cases of angina rheumatica. Meyer also made control experiments with streptococci obtained from normal throats, producing thereby in one case a pericarditis and in another a fatal sepsis. He also examined 6 cases of non-rheumatic anginas, and from one of these—a case of scarlatina—he isolated a streptococcus which produced joint exudates. A coccus similar to that of Meyer's was also isolated by Drs. Poynton and Paine (160) from a rheumatic tonsil. Glaser (1901) also produced sterile joint exudates in rabbits by streptococci obtained from rheumatic tonsils, a result occasionally produced by streptococci from normal throats, and more frequently by cocci isolated from various non-rheumatic forms of angina. Although the joints may contain numerous cocci, the blood and viscera in such cases may be sterile. Menzer (1902) went to work in the most orthodox fashion of isolating the organisms in pure culture from pieces of the excised tonsils, and then inoculated the cultures. He was unable to distinguish in culture streptococci from normal and from rheumatic tonsils. Cocci from 11 cases of rheumatism were inoculated into 19 rabbits in quantities of 6-8 c.c. of ascitic-bouillon cultures. In general he found that streptococci from rheumatic tonsils produce multiple sterile joint lesions and endocarditis. Occasionally, however, the joints contained cocci. Other complications were lung abscesses, pneumonia, local abscesses, and in certain cases the cocci were non-pathogenetic. Menzer's control experiments are also of importance; with streptococci from normal throats he obtained hyperæmia of joints, multiple embolic foci in heart, endocarditis and pericarditis, although blood and joints were apparently sterile; with streptococci from different forms of non-rheumatic angina he obtained in one case efflorescences on the tricuspid valve; with a streptococcus obtained from mammary pus he induced joint swellings and verrucose endocarditis; with a streptococcus from a characteristic case of septic endocarditis, multiple joint lesions ensued in which cocci were found by puncture. Later the swellings disappeared, and, when the animal was killed five weeks later, cultures therefrom remained sterile.

(*e*) *Examination of Rheumatic Nodules.*—Drs. Poynton and Paine (163)

succeeded in recovering their diplococcus from rheumatic nodules post mortem. Their method was to excise the nodule with the usual aseptic precautions, and to transplant it into milk-bouillon, obtaining on the third day a pure culture of diplococci. Neither in two nodules excised during life nor in two taken immediately after death could I find bacteria microscopically or by culture.

(*f*) *Examination of Chorea and Cerebral Rheumatism.*—Dana (1894) found diplococci in a case of chorea in which there was a chronic leptomeningitis of the brain and the upper part of the cord. In a severe case of rheumatic endocarditis and chorea, Triboulet and Coyon (200) found Achalme's bacillus forty hours after death. In two cases of chorea Apert (1898) found Triboulet's coccus. Westphal, Wassermann, and Malkoff found diplococci in the brain in the case of chorea mentioned on p. 609. Drs. Poynton and Paine (163) isolated a similar diplococcus in several cases of chorea, and in 3 cases of chorea Drs. Beaton and Walker found the same coccus, twice in the heart's blood and once in the urine.

Cases of cerebral rheumatism have not been frequently examined. In a case examined both during life and after death, Souques and Castaigne found the cerebro-spinal fluid sterile; Triboulet had a similar experience. Pic and Lesieur found Achalme's bacillus in one case, and in a second the cultures were sterile. Achalme found the cerebro-spinal fluid sterile, although the blood was rich in anaerobic spore-bearing bacilli.

(*g*) *Examination of Urine.*—Investigations into the bacteriology of the urine of cases of rheumatic fever have been carried out on an extensive scale by G. Singer, also by Chvostek, Kraus, Franz, and others with very divergent results. In 85 cases Singer obtained positive results 49 times; he found several different microbes, viz.: *Staphylococcus albus*, 93 times; *Staphylococcus aureus*, 14 times; *Staphylococcus cereus albus*, 13 times; *Streptococcus pyogenes*, 15 times; *Streptococcus conglomeratus*, 20 times; other cocci, 1 time; *B. coli*, 3 times; contaminations, 135 times. Singer's method of obtaining the urine for examination was defective technically, and Chvostek, who adopted proper precautions, obtained entirely different results, as was also the case with Kraus and Franz. With Singer's method employed on normal people, Chvostek obtained cocci 10 times out of 18 cases, and Litten found cocci in every normal case. Disinfecting the anterior part of the urethra, Menzer found in a normal male aged 17, thirty-two colonies of staphylococci, diplococci, and a diphtheroid bacillus. Drs. Poynton and Paine isolated their diplococcus from the urine, and Drs. Beaton and Walker did the same in 4 cases, viz. one of subacute rheumatism and mitral stenosis, two of acute rheumatism, and one case of chorea.

Résumé of Results in connexion with Hypotheses of Infective Pathogenesis of Rheumatic Fever.—A glance at the results described above shews that numbers of different micro-organisms have been isolated from cases of acute rheumatic fever. As far as concerns the blood, the examinations made during life have in the main yielded negative results, cultures made upon different media having remained sterile. In a certain number

of cases staphylococci, streptococci, and diplococci have been found. In the post-mortem blood examinations positive results occur with much greater frequency. Here again we find a series of cocci, and in a number of cases Achalme's bacillus. In not a few cases, even of severe endocarditis, cultures have remained sterile, and the microscope has failed to reveal the presence of microbes (Weichselbaum, Harbitz, Bulloch and Thompson). In regard to the joint lesions, *intra vitam*, examination has in the majority of cases proved negative. Post-mortem examination has shewn a number of different bacteria—mostly cocci. Rheumatic pleurisies are usually sterile. The examination of the throat lesions is manifestly unsatisfactory, and in a still greater degree the results which have been obtained in examinations of the urine. In the case of the characteristic rheumatic nodules the divergence of results is equally disappointing.

Apart from the ordinary pyogenetic cocci, the bacillus of Achalme and the diplococcus described by Triboulet and by Drs. Poynton and Paine must be specially considered in reference to the etiology of rheumatic fever.

Bacillus of Achalme.—This is a large motile Gram-staining anaerobic bacillus which forms terminal spores. Its length is subject to some variation; short in media containing milk, sugar, and glycerin, it is long in ordinary bouillon, and may actually grow into filaments. It grows between a minimum of 25° C. and a maximum of 40° C., flourishing best between 30° and 38°. Milk is curdled in twelve to fifteen hours; gelatin is liquefied, and gas-production is constant. Inoculation into animals produces a massive sero-sanguinolent œdema at the point of inoculation, with exudates into the serous cavities. Guinea-pigs are very susceptible to its action, mice much less so; rabbits react, with severe local lesions. By injecting the pleural exudates of infected guinea-pigs into rabbits, Thiroloix (194) produced a condition superficially resembling acute rheumatism, especially in its cardiac manifestations. Dr. Hewlett has pointed out that Achalme's bacillus is probably identical with *B. enteritidis sporogenes* (Klein), a view also acknowledged, with limitations, by Achalme himself, who further identifies it with *B. perfringens* of Veillon.

Diplococcus of Triboulet, Poynton and Paine. Micrococcus rheumaticus of Beaton and Ainley Walker.—The diplococci isolated by Wassermann, Triboulet, and Coyon, Drs. Poynton and Paine, Beaton and Ainley Walker, and Beattie are generally considered by these authors to be identical, and may, for the sake of brevity, be *temporarily* spoken of as *Diplococcus rheumaticus*. Triboulet described it as of variable form, but mostly as a diplococcus or in chains of 4 to 6 elements. It stains by Gram's method. On agar and gelatin it grows as small translucent colonies, and even shewed growth on potato. Milk is rapidly curdled. In fluid media Triboulet found lactic and acetic acids in quantity, along with traces of valerianic and formic acids. The coccus grew aerobically and anaerobically. In Triboulet's hands, with cocci obtained from 5 cases, the results of inoculation were negative. With the coccus obtained

from a case of chorea, one rabbit inoculated with 12 c.c. of culture shewed endocarditis, but the joints were normal.

Drs. Poynton and Paine's coccus grew best in a mixture of milk and bouillon, acidulated with lactic acid and incubated anaerobically. In their first publications they described their diplococcus as "easily decolorised" by Gram's method. The intravenous inoculation of large doses (contents of several blood-agar tubes) produced very definite and constant pathological results, including polyarthritis, bursitis, tenosynovitis, multiple valvulitis, pericarditis, plastic pleurisy and pneumonia, nodules, chorea, and even iritis (2 cases)—apparently all the classical lesions of rheumatism. In most of the lesions cocci were found by the microscope or in culture. As a result of their experiments, Drs. Poynton and Paine concluded that the diplococcus was *a* cause of rheumatic fever, and latterly (169) that it was *the* cause. The experimental joint lesions are of the nature of polyarthritis, and the exudate varies from a clear blood-stained fluid to a thick fibrino-cellular mass. The diplococci were often difficult to demonstrate in the joints.

Drs. Beaton and Ainley Walker confirmed the results of Drs. Poynton and Paine, isolating the diplococcus in 15 cases as detailed above. They found it was Gram-positive, and they concluded that in ordinary culture media there is nothing to distinguish it with certainty from *Streptococcus pyogenes.* On applying Marmorek's test they found that the *Micrococcus rheumaticus* grew in broth from which a culture of *Streptococcus pyogenes* had been filtered off. The coccus grew on very alkaline media (– 25 on Eyre's scale). On blood-agar they noted that the hæmoglobin round the colonies becomes of a rusty brown or chocolate colour. In rabbits seventeen positive results were obtained, comprising fever, wasting, monarthritis, polyarthritis, paresis of limbs, endocarditis, and septicæmia. Large doses were required to produce these results, except in cultures of passage. In a subsequent paper Dr. Ainley Walker and Mr. Ryffel found that relatively large quantities of formic acid were generated in cultures of the micrococcus, and they also found appreciable quantities of the same acid in the urine of those suffering from rheumatic fever, whereas in normal urine it is absent or present only in traces (v. Jaksch); under salicylate treatment the amount of formic acid diminished. The origin of the formic acid they attributed to oxidation of sarcolactic acid—$CH_3CHOH.COOH + O = CH_3COOH + H.COOH$. Dr. W. V. Shaw inoculated monkeys with cocci isolated by Wassermann, Poynton, and Ainley Walker. In one case a transient arthritis supervened in twelve hours after inoculation; in another he noted polyarthritis, pericarditis, endocarditis, myocarditis, hæmorrhagic infarcts of kidney, bronchopneumonia, enlargement of the spleen, and death on the fourth day. In the third experiment polyarthritis was followed by a mitral systolic murmur, but the animal recovered.

Lewis and Longcope's diplococcus (*vide* p. 610), in doses of 1 c.c. and 2 c.c. respectively, produced arthritis in rabbits, with thick, pultaceous, creamy fluid in which cocci were found. The coccus grew well in broth

on which *Streptococcus pyogenes* had already been grown; but a streptococcus from puerperal sepsis behaved in the same way, thus throwing considerable doubt on the value of Marmorek's test for differentiating streptococci.

The diplococcus isolated by Dr. Beattie (107) appears to be identical with those described above. He emphasised its great vitality on various media, and found that it grows best at room-temperature (20° C.), and that the growths on gelatin are relatively abundant. Anaerobic cultivation in his hands appeared to be unfavourable. By intravenous inoculation Dr. Beattie produced endocarditis, polyarthritis, and chorea, a combination of lesions similar to those in rheumatic fever in man. Dr. Beattie concludes that "*Micrococcus rheumaticus* is a special organism and is causal in acute rheumatism."

Conclusions.—From the diversity of the bacteriological results it is not surprising that even those who support the infective hypothesis should arrive at different conclusions as to the microbe or microbes concerned. These may be summed up briefly as follows:—

1. Rheumatic fever is the result of an infection with a specific anaerobic bacillus. (Achalme.)

2. Rheumatic fever owes its origin to staphylococcus and streptococcus, and is merely an attenuated form of pyæmia. (G. Singer.)

3. Rheumatic fever is not due to any particular microbe, but is a particular reaction in predisposed persons to various microbes, especially streptococci. (Menzer.)

4. Rheumatic fever is the result of an infection with a specific diplococcus. (Poynton and Paine, Ainley Walker, Beattie.)

5. Rheumatic fever is due to a virus still unknown. (Pribram, Lenhartz, and others.)

There is much against Achalme's hypothesis that rheumatic fever is caused by an anaerobic, sporing bacillus. This organism has been found in a relatively small number of cases, and then for the most part after death. It has also been found in a case of malaria (Melkich). The disease set up by its inoculation into rabbits has, with the exception of the results of Thiroloix, none of the features of rheumatic fever, but is of the type of a malignant œdema. The identity with Dr. Klein's *B. enteritidis sporogenes*, and the occurrence in rheumatism of Achalme's bacillus with other microbes, including *Bacillus coli*, is also significant of an agonal or post-mortem invasion. Singer's view that rheumatic fever is merely an attenuated staphylococcic or streptococcic pyæmia has not met with general acceptance. The very numerous positive results which he obtained, especially in the case of the urine, have not been confirmed by other investigators. His methods of examining urine for bacteria are not efficient to settle the question, and further, Chvostek and Kraus have thrown considerable doubt on the genuine rheumatic character of many of his cases. If Singer's hypothesis be accepted, it is very difficult to explain severe, rapidly fatal cases of rheumatic fever, which kill without a trace of suppuration.

Menzer's observations on rheumatism in man and his experiments on rabbits led him to an hypothesis which is difficult to disprove. According to this there is no specific virus of rheumatic fever, the disease being caused mainly by streptococci acting, so to speak, on a specific soil. The peculiarity of the soil he refers to the condition of the lymphatic apparatus, especially about the throat, and it is this which makes rheumatic fever appear to be a specific disease. Menzer considers his view is supported by the fact that streptococci occurring in the throats of rheumatic people act in the same way as those from normal people. At the same time the occurrence of streptococci in cases of rheumatic fever is very far from being constant, and, further, it is doubtful, from the observations of Pribram on 677 cases, how far the throat lesions are characteristic of acute rheumatism. In this country affections of the throat preceding or during the attack of the disease are the rule (80 per cent). In Pribram's cases there was a history of sore throat in 1·7 per cent only.

A view which meets with acceptance in several quarters at the present time is that rheumatic fever is a specific disease and is caused by a specific coccus—the *Diplococcus* or *Micrococcus rheumaticus*. This view has been largely developed in this country, and is associated mainly with the names of Drs. Poynton and Paine. It is evident from the published work that the claims for specificity of this organism must rest on the experimental results obtained by its inoculation into animals, as no other test has yet been found which will serve to differentiate it with certainty from streptococci obtained from other sources. The experimental results of Triboulet, Meyer, Menzer, Poynton and Paine, Walker and Beattie have been detailed above. It was shewn that Menzer had produced with streptococci from a mammary abscess and from a case of puerperal sepsis results identical with those he obtained with cocci obtained from rheumatic tonsils. Recently, Cole (1904) has obtained arthritis in the rabbit with six strains of streptococci isolated from cases in no way resembling rheumatism, viz. peritonitis following cancer of the stomach, puerperal fever, septicæmia, empyema, appendicitis, scarlatinal adenitis. The character of the joint lesions closely resembled the acute rheumatic polyarthritis of man, and occasionally exacerbations occurred and recoveries resulted. In two cases endocarditis was also present, affecting the mitral valve. Cole was unable to produce chorea, although this result has been described by Dr. Poynton (164) and by Dr. Beattie (108). The descriptions of the choreic condition are, however, so brief that it is difficult to form an estimate of the actual process. The observations of Menzer and of Cole throw considerable doubt on the specific character of the so-called *Micrococcus rheumaticus*; but apart from this it is remarkable that this diplococcus is so difficult to isolate that a considerable number of competent observers have failed to find any microbe in cases of rheumatism, and this applies not only to examinations of joint-fluids and blood during life, but also to the blood and heart lesions after death. In conjunction with

Dr. Theodore Thompson I have recently examined at the London Hospital 20 cases of characteristic rheumatic fever with constant negative results. Five of the cases were examined soon after death, and in spite of most careful search in the heart-blood, pericardial fluid, pericardium, endocardium, and in vegetations and nodules, both by the microscope and by cultivation, no microbes were found. In one case in which the autopsy was made forty-one hours after death the heart-blood contained a characteristic pneumococcus. It is difficult to understand such results if acute rheumatism be due to a micrococcus which admittedly grows well on gelatin at a temperature of 20° C. The large number of negative results obtained in cases of rheumatism suggest rather that this microbe is only occasionally present, and a complication of the rheumatic process—a view held by Triboulet, who himself was one of the first to study the coccus in question. Another alternative is to suppose that rheumatism is not an entity and in certain cases can be caused by the *Micrococcus rheumaticus*. This was a view originally held by Drs. Poynton and Paine (160) as a result of their earlier work. In their most recent publication (169) (1905) they appear to have altered their position, in so far that while admitting that rheumatic fever is a specific disease and that the diplococcus is the only bacterial cause of the specific disease, the coccus itself need not be specific.

In any case it cannot be held as proved that the *Micrococcus rheumaticus* is the cause of rheumatic fever, as it does not fulfil all or indeed any of Koch's so-called postulates. It is not found in every case of the disease, and the effects which it produces experimentally do not differ essentially from those produced by cocci which have been isolated from cases having nothing to do with rheumatic fever. In spite of the numerous investigations which have been carried out, it seems to me that the etiology of rheumatic fever still belongs to the arcana of pathology, and, although what clinicians call rheumatic fever is probably a specific infective disease, the virus is not known. W. Bulloch.

Symptoms.—*The onset* of rheumatic fever is in most cases gradual; a few days of malaise, accompanied by pains in the limbs and frequently associated with slight sore throat, is a common mode: well-marked rigors are unusual, but chilliness is often complained of; the temperature is raised; appetite is lost; the tongue becomes furred, often thickly coated, in severe cases the tip and edges may be red, but in milder cases are pallid and the whole organ flabby and indented at its edges by the teeth. Pain usually begins in one of the larger joints—the knee, hip, elbow, ankle, or shoulder.

With the appearance of pain and swelling in the joints the fever increases; the temperature may rise to 103° F. or more, but in hospital practice the vast majority of patients when admitted have a temperature varying between 101° and 103° F. The face is flushed; the pulse becomes more frequent and is usually full and strong; thirst increases, and there is complete anorexia; constipation is usually present. The

severity of the pain prevents sleep; delirium is rare, even in severe cases. The joint or joints first affected may remain the seat of pain or recover; but by the third or fourth day from the beginning of the illness pain and swelling have commonly attacked several joints in succession, the pain passing off in one as it increases in another: in this way nearly all the larger joints of the extremities may be affected; more rarely the sternoclavicular and intervertebral joints also suffer.

One of the most striking features of the disease is the condition of the skin. Notwithstanding the pyrexia, the skin does not feel hot to the touch; except in hyperpyrexia, it is moist and perspiring, and in by far the greater number of cases the sweating is excessive. The urine from the first is high-coloured, scanty, of high specific gravity, strongly acid, and deposits on cooling a copious precipitate of urates; not infrequently it contains crystals of uric acid. When the fever is at its height a small quantity of albumin is often present in it. The *duration* of the fever is variable; in previously healthy young adults, provided they escape pericarditis or severe endocarditis, the acute symptoms, when uninfluenced by drugs, frequently subside in eight or nine days, and convalescence is established in another ten days.[1]

Such, very briefly, is the clinical aspect of the onset and course of rheumatic fever of moderate severity, unaccompanied by either cardiac or pulmonary complications. It is necessary, however, to examine a little more closely into its course and the symptoms presented.

Though the *onset* is usually gradual, it is occasionally quite sudden. I have known it appear with excruciating pain coming on suddenly in a joint, and incapacitating the sufferer from walking home. In cases occurring suddenly after unusual exposure rigors are not uncommon; they are often frequent and of moderate severity. Whilst the duration of the fever in uncomplicated and favourable cases may be as above stated, much more commonly it runs a protracted course, the acute symptoms subsiding and recrudescing again and again. The occurrence of genuine *relapses* is also common under any form of treatment; among my own 859 cases 127, or 14·78 per cent, had relapses,[2] which occurred with nearly equal frequency in first and second attacks, but were less often met with in third or subsequent ones. Age, under forty, appears to have little influence; as in

34	patients under	10 years of age	5	relapsed	= 17·64 per cent.
315	,,	20 ,,	46	,,	= 14·60 ,,
297	,,	30 ,,	43	,,	= 14·47 ,,
140	,,	40 ,,	29	,,	= 20·71 ,,
46	,,	50 ,,	3	,,	= 6·52 ,,
27	,,	over 50, or age not stated,	1	,,	= 3·70 ,,

The average stay of patients in hospital is a very imperfect guide to

[1] *Vide* Sir William Gull and Dr. Sutton's paper (44).

[2] This average of relapses is considerably lower than that given as occurring in Guy's Hospital in cases treated with salicylates or its allies (27). This may be due to my not considering a mere recurrence of pain without a rise in temperature as a relapse.

the duration of the disease; a few prolonged cases greatly increase the average of the whole. I find that for my own cases the average stay has been thirty-two days, and that neither age nor the occurrence of previous attacks has much effect in increasing or reducing the length of their stay in hospital.

The *temperature* rises rapidly with the joint pains. Wunderlich truly remarks that "in an overwhelming majority of hospital cases the maximum temperature is reached either on the day of admission or almost directly after." My observation completely agrees with this, and there can be but little doubt that it is due to the fatigue and distress caused to the sufferers by their removal to hospital; 499 had on the evening of the day of admission a temperature between 101° and 103° F.; in 142 the temperature was between 103° and 104°, and in only twenty-three did it exceed 104° F. In the large majority of the cases these were the highest temperatures recorded during their attack. The temperature, excepting in cases of hyperpyrexia, is highest in the evening. The advent of pericarditis or severe endocarditis is generally, though by no means invariably, marked by a rise in temperature; and the same may be said of pneumonia or pleurisy. When treated with salicylates the temperature of the patients has seldom remained above the normal after the fourth or fifth day in hospital, and in a large number of the cases it sinks to normal in from forty-eight to seventy-two hours.

Sleeplessness, which is very commonly complained of, results rather from the severity of the pain in the joints than from mental excitability; and as soon as the pain is relieved complaints of want of sleep are seldom made. Delirium is exceptional; in those who have been guilty of alcoholic excesses one occasionally meets with a condition resembling delirium tremens. In a few cases, chiefly among women, the salicylate treatment pushed too freely has produced some slight wandering of mind.

Joints.—The affected joints are swollen, the skin over them has a florid blush, and serous exudation takes place into their cavities, into the tissues surrounding them, or into both. Even when neither redness nor swelling is perceptible, so long as a joint is in pain increased heat can usually be perceived by the hand laid on it. When in pain the joints are kept by the sufferers in characteristic positions: the knees slightly flexed, the ankles extended, the elbows flexed, the wrists extended, and the fingers of the hand slightly turned towards the ulnar side of the limb. One of the most characteristic features of the disease is the migratory nature of the joint affection. The joint which one day is swollen, red, and acutely painful may on the following day be free from pain and only a little stiff on movement; whilst others, normal on the preceding day, are now the seat of swelling and violent pain. The swollen tissues round the joint seldom pit on pressure, and desquamation of the epidermis does not occur, as is so frequently the case after acute gout. The cases of suppuration of the joints described by the older pathologists we now know were due in most instances to pyæmia, in some to gonorrhœal arthritis.

The condition of the *skin* is remarkable, the patients sweat most profusely; even now, when it is no longer the custom to heap unnecessary blankets on the perspiring sufferers, excessive sweating is one of their most frequent complaints. Beads of perspiration collect on the forehead and temples, and run down into the eyes, adding to their discomfort; and the extremities perspire as profusely as the head and body. Very different statements have been made as to the chemical reaction of *the perspiration*. It is commonly said to have a sour smell and acid reaction; of the sour smell about rheumatic patients there can be no doubt, and that it is due to excessive perspiration is equally true; but that this is caused by any abnormal constituents in the perspiration is at present not proved; should Dr. Ainley Walker's and Mr. Ryffel's statement that formic acid is invariably present in the urine of these patients be confirmed, it is probable that the same acid may be present in the sweat; but apart from this explanation the fermentative changes which take place in the perspiration after it is poured out would, I think, account for the odour. Exactly the same smell is present about persons in perfect health who do not change their underclothes after free perspiration induced by exercise and physical labour. Normal sweat is such a complex substance, and differs so greatly with the parts of the body where it is secreted, that little value is to be attached to observations recorded in rheumatic fever; according to my own experience, based upon a large number of observations made upon carefully cleaned skin; the perspiration on the face and chest is usually feebly acid, as it is in ordinary circumstances in health.

In connexion with the excessive sweating sudamina (15) are of frequent occurrence; they are essentially the same as those which occur in scarlatina, typhoid, and other febrile states accompanied by free sweating; but they do not run quite the same course. In rheumatism they go through changes rarely if ever seen in other conditions. The vesicles, at first clear and in fact only visible in certain lights, become much more perceptible, their contents become milky and opaque, and their bases are surrounded by a minute ring of redness. Senator, speaking of sudamina, says "they are often associated with miliaria rubra undoubtedly caused by the irritating effect of the copious secretion on the skin." I feel sure that the vesicles of miliaria rubra in rheumatism are the later stage of sudamina. The contents of the vesicles in the clear stage give an acid reaction to litmus paper; after becoming milky they are usually, if not always, neutral or feebly alkaline.

Urine.—The older researches into the condition of the urine in rheumatic fever threw no light on the nature of the disease. The urine presented the same general features as in other pyrexial states. Dr. Ainley Walker and Mr. Ryffel have lately shewn that formic acid in appreciable quantities is constantly present in the urine during rheumatic fever, while it is absent or occurs in traces only in normal urine. They find also that formic acid is obtainable from the tissues of rabbits suffering from acute arthritis due to inoculation of the *Micrococcus*

rheumaticus, and that the amount of formic acid present when salicylates are being taken is less than when none is being taken. The urine presents the same features as in other pyrexial conditions. Notwithstanding that patients are kept on a fluid diet, and that the thirst almost always present induces them to drink freely, the excessive loss of water by sweating usually reduces the quantity of urine passed below the normal amount. In colour it is a reddish-yellow of varying intensity, and the specific gravity high (from 1020 to 1030); it is clear when first passed, and, unless the patient be under treatment, invariably deposits on cooling a heavy precipitate of pinkish or fawn-coloured urates; crystals of uric acid are not infrequent. The heightened colour of the urine depends on the presence of a large quantity of hæmatoporphyrin and a small quantity of urobilin. Dr. Garrod (39) failed to find any relation between the severity of the rheumatic attacks, or the destruction of blood-corpuscles, and the amount of the colouring matter. The high specific gravity is due, not to an increase in the total amount of solids excreted, but to the diminished quantity of water passed. Senator states that the amount of urea passed exceeds the normal, notwithstanding that the diet may be very poor in albuminous substances. In cases treated by blistering fibrinuria has been observed.

Complications.[1]—Endocarditis, pericarditis, and, in less degree, myocarditis, can hardly be considered complications of acute rheumatism; they are just as much part of the disease as the affection of the joints. As certain joints escape, so in some cases no affection of the lining or investing membrane or of the muscular tissue of the heart occurs. The statistics of the frequency with which the different structures of the heart are involved in the disease are bewildering; partly from their numbers, partly from the different modes in which they have been drawn up, the majority of them having been collected to prove the advantage of some particular mode of treatment. I shall therefore confine myself to my own experience.

Endocarditis affects the sexes equally. It is difficult, perhaps impossible, to determine during an attack when endocarditis begins, for it gives rise to no special symptoms; but, in a large majority of cases, if no endocardial murmur be present during the first ten days of an attack the endocardium escapes.[2]

Pericarditis.—It is usually stated that pericarditis occurs with much greater frequency in men than women; the records of St. Bartholomew's Hospital do not shew any considerable preponderance of men. In my first series of cases, 859 in number, the percentages of pericarditis were 14·87 for men and 9·95 for women, whilst in the second series, 1431 in number, the percentages for the two sexes were nearly equal, being 11·13 for men and 10·92 for women; putting the two series together,

[1] The association of palpitation and dilatation of the heart in young persons with rheumatism was (according to Dr. M. Baillie (6)) first discovered in 1780 by Dr. David Pitcairn, physician to St. Bartholomew's Hospital.

[2] On this point see also Gull and Sutton (44).

in 2290 patients, pericarditis occurred in 12·22 per cent of the male and in 10·53 of the female patients.[1] Of the 155 instances of pericarditis noted in the second series 67 or 43·29 per cent were met with in first and 88 or 56·77 per cent in second or subsequent attacks, figures which hardly bear out the generally received opinion that pericardial inflammation is more common in first than in subsequent attacks.[2] The danger to life is undoubtedly much greater in first attacks, no less than 43·29 per cent of the 67 first attacks proving fatal, whilst only 11·36 per cent of the 88 cases occurring in second or subsequent attacks were followed by death. Of the 29 fatal cases 5 were under ten years of age, 8 between ten and fifteen, 10 between fifteen and twenty. The influence of age on the incidence and fatality of pericarditis in first attacks is strikingly shewn by these figures.

The onset of pericarditis may occur at any time during the course of the fever, in this respect differing from endocarditis, and is more common in cases in which the joint affection is severe than in those whose joints are less severely and generally affected. It is often attended by no special symptoms; neither pulse, respiration, nor general condition being altered. In other cases, before any pericardial rub can be detected, an increased frequency of pulse, a sense of oppression or pain in the cardiac region sometimes increased by pressure, a rise of temperature, and an alteration in the sounds of the heart are to be observed. Clinically the important sign is not so much the presence of pericardial friction as the extent of the præcordial dulness, which is a measure of the amount of effusion present.[3] The effusion usually consists of organisable lymph, and is often very large: fluid effusion is less frequent; when present it is generally serous, and rarely becomes purulent or blood-stained. In the seventy-nine cases of paracentesis pericardii collected by Dr. S. West (84), eleven, or possibly twelve, took place in the course of rheumatic fever. In the doubtful case pus was evacuated; in all the others the effusion was serum, or blood-stained serum; and, excepting in one instance where two pints were evacuated, the amount was small. Pericarditis in cases terminating fatally is seldom unassociated with endocarditis. Clinical experience and the results of many post-mortem investigations shew that it may be recovered from without leaving serious mischief; even when the surfaces of the pericardium become adherent little harm appears to result unless the adhesions be dense and thick, or the parietal portion of the pericardium is also adherent to the pleura or wall of the chest.

Dr. Cheadle has drawn attention to the grave results of pericarditis in children, from its interference with the growth and nutrition of the heart; and Sturges to the increased risks that are occasioned by its

[1] The risk of drawing conclusions from statistics, unless the numbers are very large, is well shewn in these figures, for the inclusion of my second series of cases reduced the difference of the percentage in women from 5 to 1 per cent.

[2] These figures agreeing closely with those of Dr. Sibson (*op. cit.* p. 208), which are 41·61 for first and 58·76 for subsequent attacks.

[3] Care must be taken not to mistake dilatation of the left heart for effusion.

presence. As these conditions will be treated of in the article on "Acute Rheumatism in Children" (p. 645) I will not further allude to them.

The presence of *endocarditis* of greater or less severity is a very constant accompaniment of the disease, and forms its most serious feature, as it leads to lasting and progressive morbid changes in the cardiac valves. The endocardium over the mitral valve is especially prone to be attacked. Affections of the aortic valves alone are, comparatively speaking, rare; when they are involved, disease of the mitral valves is almost always present (73). Endocarditis, either recent or old, was noted in about one-half of my own cases. The liability to endocarditis diminishes with the age. Dr. David Pitcairn's original observations on the connexion between palpitation, dilatation of the heart, and rheumatism related to young persons; and Sir Thomas Watson says, "I have known only three persons pass through acute rheumatism with an untouched heart prior to the age of puberty, and in two of them I am by no means certain that the articular disease was true rheumatism." My own experience is very much the same. Among my hospital cases, in

36 under 10 years of age	29	had signs of old or recent	endocarditis	=80·55	per cent.
309 ,, 20 ..	223	,,	,,	=72·16	,,
297 ,, 30 ..	159	,,	,,	=53·53	,,
143 ,, 40 ..	58	,,	,,	=40·55	,,
92 over 40 ..	19	,,	,,	=34·64	,,
12 age not stated	6	,,	,,	=50·00	,,
889	494	,,	,,	=57·50	,,

Taking first attacks, the percentage remains much the same during the first two decades, but decreases notably afterwards.

In 16 cases under	10 years of age	endocarditis	was present in	12=75·00	per cent.
.. 109 ,,	between 10 and 20	,,	,,	,,	60=54·13	,,
.. 75 ,,	,, 20 ,, 30	,,	,,	,,	38=30·66	,,
.. 36 ,,	,, 30 ,, 40	,,	,,	,,	13=33·33	,,
.. 8 ,,	over 40	,,	,,	,,	1=12·50	,,
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In two of the four patients under ten, who are tabulated as escaping endocarditis, pericarditis occurred; but the sounds and size of the heart were normal on discharge from hospital. The above figures shew very strikingly that rheumatic fever is a disease of youth and early adult life, and that the younger the sufferers the greater the liability to cardiac implication.

Myocarditis.—It is probable that in all but the slightest cases of pericarditis a certain amount of myocarditis is present. Dr. S. West (85) has drawn attention to *dilatation of the heart* occurring in rheumatic fever, or as an early sequel of it; and he has recorded a case in which well-marked symptoms of cardiac failure occurred without any evidence of endo- or pericarditis. A fatal case was met with, at St. Thomas's

Hospital, in which acute granular degeneration of the muscular tissue was found after death; but in this instance pericarditis was present also. Somewhat similar cases were recorded by Maclagan. Drs. Lees and Poynton have shewn the frequency with which dilatation of the heart is found in rheumatism and chorea in children and young persons, and consider it evidence that in rheumatism there is some toxic action exerted on the cardiac muscle, enfeebling it. Among my own cases I have met with a few in which an increased area of cardiac dulness, feeble first sound of the heart, and weakness of the pulse, have been present without any evidence of valvular or pericardial lesion; but how far the condition was due to an acute change in the heart's muscle I cannot venture to say. Rheumatic myocarditis, apart from peri- or endocarditis, I have never seen in the post-mortem room.

The clinical course and the effects of rheumatic inflammation of the heart and its coverings in young children differ in many respects from what we meet with in adults. The same may be said of rheumatic fever itself; for in young children the fever, as measured by the temperature, is seldom high, and the articular pains are slight. As acute rheumatism in young children will form a separate article in this work (p. 645), the subject will not be further considered here. After the age of twelve or fourteen the symptoms present resemble those of adults.

The other complications of rheumatic fever, with the exception of hyperpyrexia, require but little comment. *Pneumonia* and *pleurisy* are the two most important concurrent conditions; and the former presents clinical features in rheumatic patients which differ from those ordinarily accompanying it. The amount of consolidation is often considerable, whilst cough is infrequent, and there is little or no expectoration. Pleurisy occasionally leads on to effusion, but among all my cases I have only once had to tap the chest. Pneumonia occurs more frequently than pleurisy, and is very generally an accompaniment of pericarditis. Statistics of the frequency of these complications are given by many observers, but differ widely. The proportionate numbers are much higher in the older tables than in the later ones, owing to the inclusion in them of pyæmic and septicæmic cases (38). *Bronchitis*, in anything like an acute form, has been rarer among my cases than pleurisy. *Tonsillitis* is not an infrequent precursor of or concomitant with an attack. *Exanthems* of various sorts are common; in my 1431 cases I find erythematous rashes noted as present in 26; purpuric ones in 16; erythema nodosum in 10.

A consideration of the affinity between acute rheumatism and chorea does not fall within the limits of this article. During the acute stage chorea is not common, but it is met with most usually in connexion with pericarditis. It was present, in the second series of 1431 cases, in six girls, the eldest of whom was fifteen, and in eleven boys, one being eighteen, the rest under twelve years of age. Among the cases in which chorea has been present during the acute stage, several have been in young men beyond the age at which chorea is usually seen in the male sex. Two were under my own care, and the chorea, which was very

severe, came on very shortly after pericarditis had set in. Conversely a girl was admitted into my ward with chorea, heart-murmur, and no joint affection, in whom hyperpyrexia supervened and ended fatally. After death a small patch of lymph was found on the surface of the left ventricle, and many vegetations on the margins of the mitral and aortic valves.

During the course of scarlet fever, and the period of convalescence from it, pain and swelling in the joints may arise (*vide* p. 456).

Hyperpyrexia.—Since the regular use of the clinical thermometer the nature of the cases of rheumatic fever characterised by marked and decided cerebral symptoms has become known. These cases were formerly thought to be due to a metastasis of the rheumatic inflammation from the joints and heart to the meninges of the brain, and were spoken of as cerebral rheumatism. Senator says, "Acute cerebral or spinal meningitis may set in," and quotes two cases, one from Lebert and one from Dr. Stretch Dowse, in support of this statement. I have referred to the case reported by the latter, and find no reason for thinking it was rheumatic. Dr. Dowse considered it to be a case of acute arachnitis in a dissolute woman exposed to great cold and hardship immediately before the beginning of her fatal illness, and he does not attribute it in any way to rheumatism. The majority of the cases formerly regarded as rheumatic meningitis were undoubtedly pyæmic; yet meningitis apparently does occur, as in the Clinical Society's report on hyperpyrexia two instances are said to have been met with among twenty-four post-mortem examinations.

Hyperpyrexia is said to occur more frequently among men than women. Taking the cases collected by Wilson Fox (32), the Committee of the Clinical Society, and myself, we have 110, sixty-three (57·27 per cent) occurring in the male, and forty-seven (42·72 per cent) in the female sex.

It is difficult to estimate the proportion cases of hyperpyrexia bear to the number of attacks at different ages; its occurrence in early childhood is as yet unknown, and the earliest age among the cases here collected was a boy of twelve (17). Of the 110 collected cases—

16	occurred in persons under	20	years of age.
50	" between	20 and 30	"
26	" "	30 " 40	"
11	" "	40 " 50	"
5	" "	50 " 60	"
2	the age was not stated.		
110			

From these figures it would appear that no period of life, except early childhood, is exempt from this complication; after the age of sixty rheumatic fever is of extreme rarity. Hyperpyrexia is met with more frequently in first attacks than in subsequent ones. Of the 110, fifty-eight (= 53·45 per cent) were in the course of a first, twenty-two of a second, eight of a third, two of a fourth or subsequent attack; whilst in twenty the number of the attack is not recorded. The liability to and

mortality from hyperpyrexia appears greater in first than in subsequent attacks.

What elevation of temperature is to be called hyperpyrexia? The Clinical Society's Committee divided the cases into three groups: those of undoubted hyperpyrexia, with temperatures of 106° F. or upwards; those shewing a marked tendency to a continued and persistent temperature of a high range (104° F.); and a third group (in which only three cases are included), in which the symptoms usually accompanying hyperpyrexia were present but without an excessive temperature. I think cases not exceeding 105° F. should hardly be considered as cases of hyperpyrexia; and in my eighteen cases I have not included any which did not exceed this standard. The danger to life is, generally speaking, in proportion to the height of the temperature, but recovery has taken place after the temperature has reached 111° F. (28).

The cases in which hyperpyrexia supervenes do not as a rule differ at the outset from others; many of them are described as being mild, until the alarming symptoms arose. In not a few of the fully reported cases the sufferers are stated to have been in a more or less depressed mental condition for some time prior to the advent of the rheumatic attack; and several authorities have expressed an opinion that these cases are met with more frequently in patients whose constitutions have been weakened by alcoholic or other excesses; but there appears to be no good evidence in support of this view.

With the rise of temperature the commonest concurrent symptoms are diminution of the pains in the joints and sometimes complete cessation of them; extreme restlessness passing into acute delirium, or drowsiness deepening later into stupor: spasm of certain groups of muscles, or general convulsions are not uncommon. The profuse sweating diminishes, and in some instances perspiration appears wholly suppressed, and the skin is intensely hot and burning to the touch. With the rise in temperature we find great acceleration of the pulse and rate of breathing. In some patients a large increase in the amount of urine passed has been noted, and not infrequently persistent and uncontrollable diarrhœa comes on. Death is almost always preceded by coma.

Although, with the advent of hyperpyrexia, it is undoubtedly true that in many cases the articular pain diminishes, or at all events is less complained of, the Clinical Society's Committee found that in many the condition of the joints remained unaltered, and that pericarditis was present in more than half; 70 per cent of those who recovered had pericarditis at the onset of hyperpyrexia, and in 42 per cent of the fatal cases the same condition was found after death.

The rise of temperature occupies a variable amount of time. The highest point may be reached within a few hours of the commencement of the symptoms; or the maximum may not be met with until several days of high temperature have passed (37). In cases which have not been treated by direct application of cold, the highest temperature is usually at the time of death; and in several instances it has been

observed to rise for a short time after death. A continuously elevated temperature, especially if it occur in a patient whose joint pains have moderated, and in whom there is no evidence of pericarditis or other complication, should give warning of the possibility of hyperpyrexia; and means should be taken to reduce the temperature. The probability of its occurrence is still further increased if, in addition to a continuously high temperature, unusual restlessness or vigilance be present.

Hyperpyrexia is most apt to arise during the second week of the fever, but instances have been known as early as the second day and as late as the twenty-ninth (18). Out of seventy-four cases in which the date of its occurrence and of the beginning of the attack was known, hyperpyrexial symptoms commenced on the seventh, eighth, or ninth day in 25 (33·7 per cent).

Causation of Hyperpyrexia.—The group of symptoms of which rapid rise in temperature to an extreme point is the most remarkable feature is not confined to rheumatism. A similar condition may be met with in small-pox, scarlatina, typhus and enteric fevers, pneumonia, and more frequently, perhaps, in pyæmia; yet there can be no doubt that hyperpyrexia arises much more frequently in acute rheumatism than in any other disease. Rheumatic hyperpyrexia appears to be more prevalent in some years than in others, so that cases are apt to occur, as it were, in runs; but there does not appear to be any direct connexion between the prevalence of rheumatic fever and the number of hyperpyrexial cases. Hyperpyrexia occurs, in London at all events, with much greater frequency in the summer months —June, July, and August (18)—than in the other portions of the year.

At present the *pathology of hyperpyrexia* is unknown. The heat-regulating mechanism of the body is in some way or other thrown out of gear, and the cerebral symptoms are probably dependent on the circulation through the brain of unduly hot blood (63, 76, 82), producing symptoms similar to those met with in abnormally high temperatures of other specific diseases and of insolatio. Andrew remarked many years ago that the suddenness of the rise of temperature is remarkably similar to what constantly occurs at the close of cerebral disease in its coarser and more common forms,—hæmorrhage, softening, meningitis, or cerebral tumour. In what way the heat-regulating centres (if they exist) are primarily affected is unknown. Lebert was in favour of the view that in acute disease, in certain circumstances, a poisonous material is formed in the body which causes paralysis of the nervous centres; others have supported the view that the increased heat due to febrile metabolism of tissue is sufficient of itself to cause paralysis of the nervous centres on which the heat-regulating mechanism depends. In whatsoever way the paralysis of the heat-regulating centres be produced, a vicious circle is set up, resulting in an overheated condition of the body and a consequent deterioration of tissue, the muscular tissue of the heart especially suffering (*vide* vol. i. p. 846 *et seq.*).

Sequels.—Besides those pertaining to the heart and its coverings the sequels of the disease are few. It has already been remarked that

it is rare for a joint to suffer permanent injury; in this respect the disease offers a strong contrast to osteo-arthritis, gonorrhœal arthritis, and gout. The most serious evil, other than cardiac mischief, which it leaves behind it is the tendency to further attacks and *anæmia*. Dr. Garrod has extended and in the main confirmed the observations of Hayem on the condition of the blood in acute rheumatism; he shews that an attack is always accompanied by a very considerable fall in the number of the red corpuscles, and that this fall takes place with great rapidity; besides the diminution of the red, both observers are agreed that there is a slight increase in the number of the white corpuscles. Dr. Garrod further remarks that in cases running a favourable course without serious pulmonary or cardiac lesions, the red corpuscles very rapidly rise to the normal standard again. Hayem states that in protracted cases the red corpuscles fall in numbers continuously, but Dr. Garrod found that having fallen to a low level the numbers of the red corpuscles remained stationary. The variations in the hæmoglobin-worth of the red corpuscles follow closely the variations in their number; but in some instances the percentage of hæmoglobin in the corpuscles continues to fall during convalescence, although the number of red corpuscles may increase. He sums up his conclusions thus (39): "The anæmia of rheumatism is of two kinds: (1) an acute oligocythæmia developing during the acute stage, and rapidly recovered from as soon as convalescence sets in; and (2) a pseudo-chlorotic condition which is developed as a sequel of the attack in a few cases, and which unless it is appropriately treated may last for a long period, the fall of worth continuing in spite of the amelioration of the patient's condition in other respects."

The appropriate treatment of these anæmic patients is the main difficulty in the management of convalescence from rheumatic fever; in other cases, simple attention to the digestion and regulation of the bowels is all that is necessary, and bark, the old remedy for acute rheumatism,[1] often appears to me of use and preferable to quinine. Anæmic patients, and those in whom there has been endo-, myo-, or pericarditis, should not be allowed to get up until they have made very considerable progress. Iron is frequently ill tolerated in the anæmic condition immediately consequent on an attack, although at a later period it may be of great benefit; cautious trial may be made of the various preparations of iron, as, if well borne, they usually relieve the anæmia quickly: in patients who are unable to take ferruginous tonics, arsenic is of use, and I have not infrequently seen great benefit from cod-liver oil.

The gravity of the *cardiac lesions* left by endocarditis frequently does not shew itself until long after convalescence has been established; it is essential, therefore, that all violent exercise or efforts calculated to strain the heart should be avoided for a considerable time after convalescence appears complete. At the same time, sufficient exercise to improve the general health and to keep up the vigorous nutrition of the heart is of the utmost importance.

[1] Used by Haygarth on the recommendation of Dr. Fothergill.

Dilatation of the stomach is not a very rare sequel of acute rheumatism, and is a grave obstacle to recovery [*vide* art. "Dilatation of the Stomach," vol. iii.]

In connexion with rheumatic fever mention must be made of *rheumatic nodules*—small, firm, subcutaneous, fibrous nodules—which are found with much greater frequency in children than in women or men. There is no doubt that subcutaneous nodules are most commonly associated with disease of the cardiac valves. In the cases collected by Sir T. Barlow and Dr. Warner, twenty-seven in number, there was but one in which cardiac disease was not well marked; nevertheless, several cases have been reported in women (13, 24, 85) in whom no morbid sound at the heart was noted, and in adults their pathological meaning and bearing on prognosis do not appear to have much value. In my second series of patients, 1431 in number, nodules are noted as present in twenty-one. The importance of their presence in young children is shewn by seven out of nine under 11 years of age who had them dying, whilst of the other twelve none died; among them were two women aged 22 and 39. For an account of these subcutaneous nodules on children, see p. 655; and for their morbid anatomy, pp. 605, 655.

The diagnosis of rheumatic fever, excepting in young children, seldom presents serious difficulty; nevertheless there are some conditions which may be mistaken for it, and occasionally it is impossible to form a differential diagnosis until the case has been under observation for some time. Osteo-arthritis in women who have been exhausted by child-bearing and lactation, and more especially in those whose recovery from childbirth has been imperfect and accompanied with uterine discharge, begins, I believe, much more frequently in an acute or subacute manner than is generally supposed. I have seen many cases beginning with slight fever and joint-pains resembling those of rheumatic fever, in which there was no tendency to cardiac affections, and no response to salicylate treatment; such patients after a time have slowly improved, but have been left with stiffness and some enlargement about the affected joints, and were destined, I fear, to become the victims of chronic osteo-arthritis. Gonorrhœal rheumatism—or, more properly, synovitis—may be recognised by the presence or history of a urethral discharge, by the condition of the affected joints, and by the fixity of the pain in them.

Pyæmia, when not secondary to some obvious form of injury, is usually due to acute necrosis or osteomyelitis of some long bone, or to disease of the petrous portion of the temporal bone, and is the state most commonly confounded with acute rheumatism. The rarity of rigors in rheumatism, and their frequency and severity in pyæmia, may prevent this error: in acute necrosis of the long bones there is usually general swelling and acute tenderness of the limb affected, together with œdema; and in disease of the petrous bone either a history of a discharge from the ear, or the presence of it, together with tenderness over the mastoid process and some puffiness about the tissues in its neighbourhood. In pyæmia the joint or joints affected remain so, and the pain and swelling do not

shift. The condition of the skin and the character of the fever are valuable guides—the skin in the pyæmic cases being often hot and burning, and rarely perspiring to the same degree as in rheumatic fever, whilst the temperature is of a hectic character. Infective or ulcerative endocarditis, which may be secondary to rheumatic affection of the valves, is frequently accompanied by pain and swelling in the joints, and may be mistaken for rheumatic fever. The enlargement of the spleen, due to infarction, and the presence of albumin or blood, or both, in the urine, due to similar conditions in the kidneys, together with the hectic character of the fever, usually prevent any difficulty in recognising this condition.

A first attack of *gout* in a young subject may be another cause of hesitation for a time, but attention to the history and the absence of cardiac mischief will leave little doubt as to the diagnosis. In babies I have known *infantile scurvy* mistaken for rheumatism (cf. p. 648); in older children the swelling and tenderness accompanying hæmorrhage into a joint in *hæmophilia* simulate rheumatism very closely. The muscular and arthritic pains accompanying the early stages of *spinal disease* are often taken to be rheumatic, but they can hardly be confounded with rheumatic fever. Among the rarer conditions which should be mentioned are *trichinosis* and *glanders*, which latter at the outset is not infrequently mistaken for rheumatic fever.

Treatment.—While we remain doubtful of the immediate cause of acute rheumatism, its treatment remains in one sense empirical. It is profitless to go at length into the various methods of treatment which have been in vogue at different times since Sydenham first clearly defined the disease, and treated it (with the great exception of bleeding) on the principles by which we are guided now; nevertheless it will be advisable to review very briefly the methods that have been used. Sydenham (76) says, "No one doubts the inflammatory nature of pleurisy, and the blood of rheumatism is as like the blood of pleurisy as one egg is like another. Hence the cure is to be sought in blood-letting." We can no longer uphold the father of modern clinical medicine in this opinion, but his rules as to regimen and diet still hold good. Nor should it be forgotten that he says (77), "With young persons and those who have not over-indulged in wine, rheumatism may be dispelled by spare and cooling diet, provided that it be moderately nourishing. This will often do as well as repeated bleedings, which are but badly borne." Sydenham's teaching and practice held their ground until the middle of the last century, and it was chiefly due to the practice and teaching of P. M. Latham, Todd, Watson, and Corrigan that the profession in this country recognised the error of venesection. Thus Latham says, "I have seldom employed venesection, and never largely"; Todd says, "My experience leads me to value very lightly the efficacy of general bleeding in inflammation of the heart"; and Watson, "I seldom open a vein in these cases." The French school at the beginning of the last century carried venesection to extreme excess, and somewhat later Bouillaud, to whom we owe much for his demonstrations of the connexion between

rheumatism and heart disease, was perhaps the greatest bleeder of them all. As bleeding fell into disuse purgation came in. Macleod, indeed, embraced both in his severe discipline; and Hope made use of calomel and opium together with salts and senna in doses sufficient to ensure four or five stools daily.

The alkaline system of treatment was brought into general prominence by Fuller, and was adopted by the bulk of practitioners in this country: though it never had the same popularity on the Continent. Founded on the conception that rheumatism was due to the presence of an acid in the blood, it was thought that if this acidity could be neutralised benefit to the patient would ensue. The alkaline treatment still has strong supporters in this country, and I think it cannot be denied that it is beneficial; by depressing the heart's action it tends to lessen the danger of the occurrence of pericarditis, and possibly of endocarditis. Its greatest benefit was that its adoption led to the diminution or abandonment of the treatment by mercurials, which had been so universally inflicted on sufferers from endo- or pericarditis.

We now can ascribe little or no therapeutic value to the lemon juice treatment first introduced by Owen Rees, and used by Lebert and others abroad. Lebert made a very careful trial of it, giving the juice in increasing doses until six ounces a day were arrived at. It appears to me hardly necessary to do more than mention colchicum, veratria, aconite, tartar emetic, quinine, and other well-known drugs, which have each in their turn been recommended on high authority; nor the more recently introduced antipyrin, phenacetin, and trimethylamine, which reduce the temperature indeed, but appear to have no really beneficial action on the disease. The marked anæmia which accompanies and follows acute rheumatism led to the administration of iron, especially the perchloride; but experience has shewn that in the acute stage it is useless if not injurious.

The general experience that the fever and the pain in the joints are increased by movement, has led to the method of treating these cases by mechanical fixation of the joints with plaster of Paris or starch bandages; good results are said to have followed this plan, but I have no experience of it myself, and it has been little tried in this country. For a time the treatment by blistering over or near the affected joints, so strongly advocated by Davies, was in favour; but no one, I think, would now maintain that it was of any assistance in the elimination of the morbid matter. Injection of various substances into the tissues surrounding the affected joints has been practised: Senator speaks favourably of his experience of Kunze's method (50), of injecting a 1 per cent solution of carbolic acid; and Dr. Gillespie has recorded some cases in which a 10 per cent solution was used with marked success so far as the relief of the pain was concerned.

Esmarch and Stromeyer recommend the application of cold compresses or ice-bags, and many years ago Dr. Dover said of rheumatism: "This is likewise a highly inflammatory fever; the blood does not appear more pleuritical or sizey in any distemper than this. Bleeding in

this case is no remedy. I myself have known many lose a hundred ounces of blood and more without relief. The cure is much easier performed without that operation. Immersion in cold water is a remedy of singular use, as is evident from many hundreds that have been cured by cold water."

The use of willow bark in the treatment of intermittent and other fevers has been advocated, from time to time, for more than a hundred years (80); its virtues have been considered by some observers to be superior to those of cinchona. With the advance of chemical knowledge its active principle, salicin, was recommended for the same uses about seventy-five years ago (7), and about thirty years later salicylic acid was introduced to medical practice; at first mainly as a disinfectant. Almost simultaneously salicylic acid in Germany (69, 74) and salicin in this country were used for the treatment of acute rheumatism; and the results obtained were so favourable that the treatment of acute rheumatism by salicin, salicylic acid, or its compounds, quickly became general. The inconveniences in the use of salicylic acid were great; it is insoluble, disagreeable to take, and causes not infrequently gastric and intestinal irritation: it was soon found that its alkaline salts had the same beneficial effects without the disadvantages, and in this country salicylate of soda is used almost to the exclusion of other compounds. The addition of an equal or rather larger amount of bicarbonate to the salicylate of sodium usually prevents any unpleasant effects, and appears to increase the efficiency of the drug. I have had but little experience in the use of aspirin in acute rheumatism; it is stated to be better tolerated than salicylic acid or the salicylates, and to be of great value. In cases of chronic rheumatic pain and gout it has appeared to me of decided benefit.

I have seldom, if ever, seen serious or alarming symptoms produced by salicylate of soda, similar to those described by Greenhow, and alluded to by Sir William Broadbent and others, when due care was taken to diminish the quantity given as its effects are manifested. In cases of pericarditis, where myocarditis may be present without our knowledge, caution must be exercised in the use of salicylate, and the force and frequency of the pulse be noted at frequent intervals. Cerebral symptoms have been more frequently observed, not only the deafness, singing in the ears, buzzing and sound of rushing of water in the head which occur whenever the drug is pushed a little too far, but decided wandering of the mind. This has occurred in my experience more frequently in women than in men, and has occasionally taken place before the patients appeared to be fully under the influence of the drug.

Experience shews that the most favourable treatment for cases of ordinary severity is as follows:—Twenty-grain doses of salicylate of soda every two or three hours until the patient is fully under the influence of the drug and the pain in the joints relieved, which usually happens in twenty-four hours or less; the drug should then be reduced in quantity, and as soon as the pain is gone and the temperature fallen to normal, the amount should be further reduced to half a drachm or a drachm in the twenty-four hours. This small dose should be continued for ten to

fourteen days, as its continued administration appears to have a decidedly beneficial effect in warding off relapses.

I fear that, notwithstanding the marked relief that patients obtain from treatment with salicylates, we cannot regard them as specific remedies; cardiac complications appear as common now as of old, and relapses are as frequent.

If the tongue be coated and the bowels constipated, a free purgative of calomel, or calomel and colocynth, followed if necessary by sulphate of magnesia, is advisable; a free action of the bowels at the commencement of the salicylate treatment appears in great measure to obviate the unpleasant cerebral effects of the drug.

The diet should be fluid, and consist mainly of milk and farinaceous compounds, such as arrowroot, corn-flour, rice, and so forth. A moderate amount of beef-tea or other animal broths may be allowed. I have never seen advantage from rigidly cutting off all animal broths, as recommended by some writers (1). Plain water, barley water, lemonade, or imperial drink may be allowed at will to assuage the thirst from which the patients, notwithstanding their fluid diet, usually suffer. As a general rule, alcoholic stimulants are to be avoided; but in cases of prostration benefit is obtained from the administration of small quantities (not more than one to three ounces) of brandy in the twenty-four hours.

In cases complicated with severe endo- or pericarditis stimulants are more frequently required, and the diet must be more generous—eggs beaten up with milk and brandy, and a large quantity of animal soups, being advisable.

Rest is most important, and for this purpose attention should be paid to the bed, which should be flat, smooth, and not too soft. Feather-beds are to be avoided, and the patient should be lightly clothed. Perspiration is so abundant that the sufferers are more comfortable when lying on a blanket than on linen, and they should wear flannel or merino bedgowns.

The existence of endo- or pericarditis calls for no special change of treatment. If in pericarditis much pain be present, a comparatively rare event, the application of a few leeches to the præcordia usually relieves it; where discomfort and oppression are present rather than acute pain, a blister is of use; and blistering appears to favour absorption of the effusion. Dr. Lees speaks most favourably of the application of ice to the chest in pericarditis. In his experience it tends, when applied continuously to the chest, to check the violence of the local inflammation, hinders effusion, helps to cause absorption, diminishes the dilatation of the heart, and is usually grateful to the feelings of the patient. I have no experience of its use in pericarditis; in croupous pneumonia it appears to me an uncertain mode of treatment; some patients like it and are relieved by it, but many are not able to tolerate it. No one now believes in the efficacy of mercury in controlling rheumatic pericarditis. It used to be given by the physicians of former generations in conjunction with opium; and I am convinced that in many cases in which dyspnœa and restlessness occur, marked benefit is obtained from

the moderate and judicious administration of opium, which in these cases I prefer to morphine.

In the treatment of endocarditis endeavour should be made to give the heart as little work to do as possible. In addition to perfect rest in bed, Dr. Caton speaks favourably of the results he has obtained by simultaneously giving sodium or potassium iodide, and frequently applying small blisters to the chest.

The pain and swelling around the joints are so capricious, and move so rapidly from joint to joint when no applications are made to them, that it appears doubtful whether topical applications have much effect either in relieving the pain or influencing the disease. Fomentations and all wet applications are troublesome and not to be recommended; belladonna or opium liniment applied on lint, covered with oil-silk, sometimes appears of service, or wrapping the joints in simple cotton-wool. It has lately been stated that oil of wintergreen, or salicylic acid, lanoline, oil of turpentine, of each one part, with lard, ten parts, applied externally to the joints act as well as when taken internally, being absorbed by the skin. In the few cases in which I have used this application, I have failed to find any evidence of absorption of salicylic acid as tested by its presence in the urine; and I have not seen any benefit to the patient. When tenderness and stiffness remain about a joint much relief may be obtained from properly directed passive movements and rubbing. Acute rheumatism rarely injures a joint permanently; and when ankylosis or persistent stiffness results, in all probability the original disease was not acute rheumatism.

Treatment of Hyperpyrexia.—Experience has shewn that in these cases, as in insolatio, no antipyretic drugs are of any use. The only successful mode of treatment is the rapid abstraction of heat, and by this means we are able to snatch some sufferers from the very jaws of death. Meding appears to have been the first to save life in this way—in the case of a woman in whom hyperpyrexia occurred about the twentieth day of an attack of rheumatic fever following erysipelas. The rheumatic attack was of moderate severity and complicated with endocarditis; the temperature rose to 108·6° F. In the same year Wilson Fox (33) published his first case treated unsuccessfully by repeated immersion in cold and tepid baths, and the following year his two successful ones (34). Although the value of cold affusion in the treatment of fevers had been recognised for years, and its efficacy in insolatio had been proved by Morehead and others of large Indian experience, it was not until after the publication of Wilson Fox's cases that the treatment of hyperpyrexia by the rapid abstraction of heat was systematically used in this country. Prolonged experience has proved its efficacy not only in "rheumatic," but also in other forms of pyrexia; and many lives have been saved by this means. When this mode of treatment was first made use of, the patients were placed in baths of 90° F. or higher, and the water gradually cooled. Experience has shewn that nothing was gained by this, the temperature of the bath need not be raised above 65° F.—the more rapidly heat can be extracted from the patient the better, and the less the subsequent exhaustion;

hence it is a good plan to add ice rather than water of the temperature of the air to the bath as it is heated by the patient. Cold-water packing alone is not of much effect; but ice-packing and rubbing the body with lumps of ice have secured results nearly as satisfactory as the cold bath, and can be applied when facilities for bathing are not at hand. Care should be taken to sponge the head with ice-cold water or to apply an ice-cap whilst the patient is in the bath. The duration of the bath depends on the rapidity of the fall in temperature and the condition of the patient. It is desirable, if possible, to keep the patient in the bath until the temperature has fallen five or six degrees. If decided shivering comes on, the patient must be taken out of the bath, even if the temperature has not fallen many degrees; not infrequently the temperature continues to fall for a time after removal from the bath. To combat the collapse which sometimes follows, the free use of stimulants is required; and should the temperature sink below the normal, and blueness and lividity of the face or extremities remain, hot bottles should be applied to the feet and back. Abstraction of heat being the only method as yet known of benefiting these patients, the cold bath must be repeated as often as necessity arises; patients have recovered after undergoing twenty-six baths; in one case during thirteen, in another during sixteen days (17).

The presence of pneumonia or of peri- or endocarditis, though probably adding to the danger of a fatal issue, does not in any way contra-indicate the use of the cold bath.

It is difficult to form an estimate of the proportionate number of cases of hyperpyrexia which are saved by this treatment, as the fatal cases are not reported so freely as those in which recovery takes place. The mortality of the collected cases to which reference has been made was as follows:—

	Cases.	Deaths.	Recoveries.
Clinical Society's Report	67	33	34
Wilson Fox's cases	22	19	3
Other cases collected by the Author	21	8	13
	110	60	50

Omitting 18 cases of Wilson Fox's collected cases, in which the application of cold was not tried, there remain 92—42 deaths and 50 recoveries.

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Serum Treatment.—Assuming that rheumatic fever is caused by a streptococcus, Menzer has prepared a serum by inoculating horses with living cultures obtained directly from human cases. This serum is supplied by Merck and described as Menzer's serum. Its action is stated to be bacteriolytic, but no experimental proof has been adduced that this is so. The method by which the strength of the serum is standardised is also unsatisfactory, a "normal" serum being such that if

1 c.c. is injected subcutaneously it will produce in chronic streptococcus infections in man a distinct local and general reaction. For cases of rheumatic fever Menzer recommends daily injections of 5-10 c.c. up to a total dose of 50 c.c., with intervals of one or two days in cases of high fever.

From the results of his treatment of a considerable number of cases, Menzer concludes that the serum treatment of rheumatic fever gives better results than any other method, in so far that there is less chance of the development of a chronic rheumatism, and that the frequence of endocarditis and relapses is diminished. These views are not confirmed by the observations of Sinnhüber or Bibergeil, although they noted some improvement in chronic cases. W. B.

The appendices need a few words of explanation and comment.

Dr. Newsholme, in the Milroy Lectures of the year 1895, when dealing with the returns of the Army Medical Department, did not separate rheumatism from rheumatic fever. An examination of the figures in Appendix II. shews how necessary it is that this should be done in estimating the frequency of rheumatic fever at any station; as it will be seen that at some stations where the admissions for rheumatism are high no case of rheumatic fever was met with. In Appendix I. I give the proportion of deaths from rheumatic fever and rheumatism of the heart in every 1000 deaths in the United Kingdom and in some of our Colonies. Vital statistics are not kept in the same form in all our Colonies, which renders it difficult to compare their figures with those for this country; the same difficulty is also met with in endeavouring to compare the returns of foreign countries with our own. The figures given apply to rheumatic fever or acute rheumatism, no such term as rheumatism of the heart occurring in the foreign returns. In Dr. Newsholme's Milroy Lectures a very large amount of statistical information as to the mortality and occurrence of rheumatic fever is given. The figures given in the table are for years subsequent to those collected by Dr. Newsholme. By the kindness of the Director-General I was furnished with the figures placed in the second column of Appendix II., which shew the amount of rheumatic fever in the army during the years 1889-91. In giving the returns for 1903, which can be obtained from the "Report on the Health and Sanitary Condition of the Army," prefixed to the statistical tables, I have thought it desirable to give the total number of men at the various stations, as the ratio per 1000 of strength in stations where the numbers are small gives an incorrect impression of the frequency of the disease.

Appendices III. and IV. are republished in their original form. I attach little importance to IV. It is roughly in accordance with the returns of the Registrar-General, which shew that the mortality from rheumatic fever and rheumatism of the heart is greater in the north-western division and in the large centres of population than in the other divisions of the kingdom. The east coast appears to suffer decidedly less than the west; Newcastle-on-Tyne, which is a vast manufacturing city, is alone in presenting a high average. In compiling this list, care was taken to make

use only of the returns of those hospitals which afforded full information as to the actual numbers of their rheumatic fever or acute rheumatism cases; and of the annual number of their medical as distinguished from their surgical patients. I am glad of this opportunity of tendering my thanks to the secretaries and resident officers who have so kindly supplied me with the information which enables me to compile Appendices IV. and V., at a trouble and labour to themselves which I fear was considerable.

APPENDIX I.—Shewing the Ratio of Deaths attributed to Rheumatic Fever in every 1000 Deaths in various Countries.

Stations.	Ratio of Deaths from Rheumatic Fever per 1000 of Deaths.	Remarks.
		Years.
England and Wales	4·62	1903.
Scotland	3·78	,,
Ireland	2·75	,,
New South Wales	4·48	,, Average for 6 years, 4·03.
Western Australia	2·72	,,
Victoria	1·69	,, Average for 10 years, 1891-1900, 5·30.
Tasmania	6·18	,,
New Zealand	4·69	,,
British Columbia	4·45	,,
Jamaica	1·64	,, For the European population only.
Straits Settlements	0·27	1904. For the whole population of all nationalities.
Queensland	13·70	1903. For rheumatism, gout, and arthritis grouped together.
Ceylon	6·78	,, For all forms of rheumatism in the whole population.
Mauritius	1·33	,, For all forms of rheumatism in the whole population.
Honduras	1·01	,, For all forms of rheumatism in the whole population.
Denmark	1·10	Average for 10 years, 1894-1903.—Max. (1897), 1·42; min. (1902), 0·71.
Italy	1·21	Average for 9 years, 1894-1902.—Max. (1899), 1·38; min. (1894), 1·06.
Norway	2·86	Average for 10 years, 1894-1903.—Max. (1902), 3·11; min. (1894), 1·98.
Prussia	2·37	Average for 9 years, 1894-1902.—Max. (1902), 2·75; min. (1898), 2·22.
Large Cities		
Berlin	2·38	Average for 11 years, 1894-1904.—Max. (1900), 3·53; min. (1894), 1·42.
Christiania	2·35	Average for 11 years, 1894-1904.—Max. (1903), 3·55; min. (1904), 1·29.
Copenhagen	3·23	Average for 11 years, 1894-1904.—Max. (1897), 5·02; min. (1902), 0·97.
Paris	1·91	Average for 3 years, 1901-1903.—Max. (1903), 2·14; min. (1902), 1·75.
New York City and Brooklyn	3·48	Average for 6 years prior to 1894.

APPENDIX II.—Abstracted from the Army Medical Reports, shewing the average Number of Admissions to Hospital for Rheumatism and Rheumatic Fever per 1000 of strength at the various stations prior to 1894, the ratio of admissions per 1000 of strength for Rheumatism during 1903, the actual number of men at the various stations, and the number of admissions for Rheumatic Fever during 1903.

Stations.	Average No. of Admissions to Hospital per 1000 of Strength for Rheumatism prior to 1894.	Ratio of Rheumatic Fever to 1000 of Strength prior to 1894.	Actual No. of Men at various Stations, 1903.	Ratio of Admissions to Hospital for Rheumatism per 1000 of Strength, 1894-1903.	Actual No. of Cases of Rheumatic Fever occurring.	Remarks.
Gibraltar	35·18	2·38	4689	21·7	11	= Ratio of 2·3 per 1000 of strength. One case of rheumatic fever fatal. From 1889-91 the forces in Cyprus, now included in the Egyptian garrison, were included in the Gibraltar force.
Malta	29·91	3·71	9313	20·7	4	
Malta Artillery	...	...	706	17·3	...	
Canada	31·9	2·83	1986	22·2	1	
Bermuda	16·18	0·42	2577	16·0	..	
Non-European Troops	...	...	202	25·0	1	
Barbadoes	63·15	...	882	39·7	...	
Non-European Troops	...	...	656	53·5	2	One case fatal. The non-European troops in the West Indies prior to 1889 gave 33·42 as the ratio for rheumatism and 1·75 for rheumatic fever.

Jamaica	33·42	0·83	564	20·9	...	
Non-European Troops	...	...	1173	31·8	...	
Western Africa	...	...	198	18·8	...	
Non-European Troops	...	0·70	2269	54·3	1	
St. Helena	42·49	1·30	405	22·9	2	The figures given in columns one and two were those for St. Helena and Cape Colony, which formed one station then.
South African Command[1]	...	...	27,680	15·4	86	= Ratio of 3·1 per 1000 of strength. Two cases fatal.
Mauritius	26·86	3·75	746	15·0	...	
Non-European Troops	...	...	1392	15·0	...	
Ceylon	28·18	...	1347	17·4	...	
Non-European Troops	...	...	219	77·0	...	
South China	...	...	1220	24·5	2	North and South China were not separated from the Straits Settlements between 1885 and 1894.
North China	...	...	472	4·2	...	
Straits Settlements	17·09	1·94	813	17·2	...	
India	32·68	2·50	69,613	26·8	35	= 0·5 per 1000 of strength. Two cases fatal.
Non-European Troops	...	0·29	124,660	...	20	= 0·1 per 1000 of strength. Two cases fatal.
Egypt and	26·79	7·02	4954	23·9	9	= 1·8 per 1000 of strength. The figures in column two are for ten years; if five years after the termination of the war be taken the ratio is 1·73.
Cyprus[2]	19·04	2·38				
England and Wales	31·06	3·43	100,246	17·4	116	= 0·8 per thousand of strength. One death ascribed to rheumatism.
Scotland	24·20	1·52	6646	19·8		
Ireland	27·90	2·03	25,379	17·3		

[1] The military statistics for the years of the late war (1899-1902) were not available at the time this table was drawn up. During the period of active service in 1880-81 the ratio of admissions to hospital for rheumatic fever was 6·48 per 1000 of strength.

[2] During the Egyptian War.

Appendix III.—Statistics of Rheumatism abstracted from the Official Returns of our Colonies and Colonial Dependencies, shewing the average Number of Cases of Rheumatism admitted to the Civil Hospitals per thousand of admissions from all causes.

Stations.	Admissions for Rheumatism per thousand of Total Admissions.	Remarks.[1]
1. Honduras	92·07	
2. Victoria (Australia)	71·32	6 years.
3. Jamaica	56·11	6 years.
4. Straits Settlements	53·95	4 years.
5. Sierra Leone	53·56	
6. New Zealand	53·33	7 years.
7. Nova Scotia	44·25	
8. Western Australia	42·71	
9. Province of Ontario	41·82	
10. Cape of Good Hope	41·10	
11. South Australia	38·44	Adelaide Hospital only.
12. Ceylon	36·30	
13. St. Helena	30·44	
14. British Guiana	28·40	
15. Victoria Hospital (Halifax)	26·45	
16. Mauritius	23·79	
17. Tasmania	23·79	
18. Malta	22·71	

[1] The averages are taken from the last five years for which I could obtain statistics, except when otherwise stated.

[Table

Appendix IV.—Shewing the Proportion of Acute Rheumatism to the Total Admissions for Medical Diseases in various Provincial Hospitals in Great Britain and Ireland.

Hospitals.	Rheumatic Fever. Per cent.		Remarks.
1. Salford	10·24	5 years	
2. Whitehaven	9·53	10 ,,	
3. Burton-on-Trent	9·26	10 ,,	
4. Barnsley	8·07	7 ,,	Victoria Hospital. Acute and subacute.
5. Tewkesbury	7·66	10 ,,	
6. Oxford	7·64	11 ,,	
7. Bristol	7·20	10 ,,	Royal Infirmary.
8. Brighton	6·74	10 ,,	
9. Leeds	6·59	7 ,,	
10. Hastings	6·56	5 ,,	
11. Sheffield	6·06	11 ,,	Approximate only. One-half of cases being stated to be acute.
12. Kilmarnock	5·75	10 ,,	
13. Birmingham	5·57	10 ,,	General Hospital.
14. Douglas, Isle of Man	5·33	9 ,,	
15. Bedford	5·14	11 ,,	
16. Dorchester	5·13	10 ,,	
17. { Glasgow	5·10	10 ,,	
17. { Newcastle-on-Tyne	5·10	5 ,,	
17. { Stoke-upon-Trent	5·10	5 ,,	
20. Newark	4·70	10 ,,	
21. Salisbury	4·68	10 ,,	
22. Derby	4·60	6 ,,	
23. Birmingham	4·28	11 ,,	Queen's Hospital.
24. { Guildford	4·17	11 ,,	
24. { West Norfolk and King's Lynn	4·17	6 ,,	
26. Hereford	4·04	10 ,,	
27. Liverpool	3·96	10 ,,	Royal Southern Hospital.
28. St. Patrick Duns	3·77	8 ,,	Dublin.
29. Exeter	3·76	3 ,,	
30. Folkestone	3·73	5 ,,	
31. West Meath and Mullingar	3·57	5 ,,	
32. Manchester	3·34	12 ,,	Royal Infirmary.
33. Dundee	3·30	8 ,,	
34. Aberdeen	2·81	8 ,,	
35. Guernsey	2·74	7 ,,	Cottage Hospital.
36. Leamington	2·64	5 ,,	Warnford Hospital.
37. Perth	2·53	3 ,,	This is calculated from an average of medical cases.
38. Kent and Canterbury	2·52	10 ,,	
39. Edinburgh	2·35	1 year	One year only.
40. Chichester	1·83	10 years	
41. East Suffolk and Ipswich	1·41	10 ,,	
42. Louth Dispensary	0·97	8 ,,	
From the following hospitals, the returns did not permit the cases of rheumatic fever to be separated from the rest of the rheumatic cases :—			
43. Torbay	12·35	9 years	All cases said to be acute.
44. Gravesend	5·96	10 ,,	
45. Liverpool	5·56	8 ,,	Majority acute. Royal General Infirmary.
46. Huntingdon	5·00	...	An average only.
47. Grantham	3·59	10 years	
48. Huddersfield	2·00	10 ,,	An average only.

Appendix V.—Shewing the average Proportions of Cases of Rheumatic Fever admitted to some of the London Hospitals to the Total Admissions to the Medical Wards.

Hospitals.	Percentage of cases of Rheumatic Fever.	Remarks.
Westminster Hospital . . .	7·37	9 years 1884-92.
St. George's Hospital . . .	6·60	10 ,, 1884-93.
University College Hospital . .	5·74	10 ,, 1881-90.
St. Thomas's Hospital . . .	6·13	10 ,, 1882-91.
St. Bartholomew's Hospital . .	6·63	21 ,, 1873-93.

If the last five years of the series is taken, a very great diminution in the number of cases at the Westminster, St. Thomas's, and St. Bartholomew's Hospitals is shewn. University College Hospital shews a fractional decrease, and St. George's a fractional increase.

Hospitals.	Percentage of cases of Rheumatic Fever.	Remarks.
Westminster Hospital . . .	3·70	5 years 1888-92.
St. Thomas's Hospital . . .	4·78	5 ,, 1887-91.
St. Bartholomew's Hospital . .	3·51	5 ,, 1889-93.
University College Hospital . .	5·22	5 ,, 1886-90.
St. George's Hospital . . .	6·22	5 ,, 1889-93.

During the last eleven years the figures remain much the same.

Hospitals.	Percentage of cases of Rheumatic Fever.	Remarks.
Westminster Hospital . . .	5·60	11 years from 1894.
St. Thomas's Hospital . . .	4·40	,,
St. Bartholomew's Hospital . .	4·64	,,
University College Hospital . .	4·00	,,
St. George's Hospital . . .	6·43	,,

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THE ACUTE RHEUMATISM OF CHILDHOOD

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Acute rheumatism, as it occurs in childhood, presents many points of difference from the disease as it appears in maturer life. The ordinary conception of acute rheumatism, as characterised by swollen, tender, painful joints, profuse sour-smelling perspiration, and high pyrexia, is drawn from observation of this affection as we see it in adults; in them arthritis is one of the most constant, prominent, and characteristic of the morbid phenomena. This description, however, does not represent rheumatism as it is usually seen in childhood; at this period of life it has a far wider pathological range, and its phenomena are more various and comprehensive.

The Rheumatic Series.—Certain affections of other parts and organs are so frequently associated with acute rheumatism of the joints that the existence of some close pathological connexion between them is now very generally accepted; and these affections appear more frequently and play a more prominent part in the disease as it is presented in childhood. Endocarditis and pericarditis, for example, which are frequent accompaniments of articular rheumatism in adults, appear yet more frequently and in more intimate association with the rheumatism of childhood. In addition to these there are other manifestations which appear so commonly or exclusively in association with rheumatism in the case of children that they must be admitted into the rheumatic series; namely, subcutaneous tendinous nodules, exudative erythema, and chorea: not to mention a few rarer conditions of less certain connexion. In the rheumatism of children these non-arthritic manifestations become

conspicuous and frequent; while articular inflammation, so prominent in the rheumatism of adults, is usually slight and unimportant, and occasionally may be absent altogether. Tonsillitis occurs in connexion with the rheumatic state in children, as in adults; but has no special features or significance.

In the case of children, then, arthritis is not the eminent or representative symptom. It would seem that at this period the joint-tissues are less susceptible, the other fibrous tissues, the skin, and the nervous system more so than in later life. Thus in the rheumatism of childhood arthritis is at its minimum; endocarditis, pericarditis, subcutaneous nodules, chorea are at their maximum. As life advances this rule is gradually reversed; the joint affection grows more prominent, regular, and characteristic, while the other phenomena decline and tend to die out. Endocarditis and pericarditis become less frequent; subcutaneous nodules, so significant in early life, practically cease with the advent of puberty; and chorea, so common in connexion with the rheumatism of childhood, almost disappears as maturity is reached. If the picture of acute rheumatism had been drawn originally from the disease as it appears in childhood, when it arises under simpler conditions, the articular affection would not have been regarded as representative; endocarditis and pericarditis, and possibly chorea, would have been looked upon as the primary and essential phenomena, and arthritis as a complication.

Another general point of distinction between the rheumatism of childhood and that of later life is the tendency of the various phases to arise independently and apart from each other. They do indeed occur together—arthritis, for example, with pericarditis and endocarditis, or endocarditis with chorea and nodules; or all these together as phenomena of the same rheumatic storm; yet the series of rheumatic events is often spread out or scattered over a term of months or years, so that the history of a rheumatism may be the history of a whole childhood. At one time, for instance, there may be an endocarditis, a chorea at another, and an arthritis at another, without any further coincident manifestation of the disease. Again, the rheumatic series, as seen in children, may be complete or incomplete in any degree. The whole series of phenomena may follow in succession, or the expression of the rheumatic attack may be limited to a single event. An arthritis, an endocarditis, or a chorea may occur alone, without the subsequent occurrence of any other rheumatic seizure. Again, the combinations of the several phases may follow any order of sequence.

Sometimes—perhaps most frequently—an arthritis appears first; in other cases an endocarditis; now and again a chorea inaugurates the morbid series. These phases may, moreover, be closely associated in point of time; or may occur singly, or again in groups with varying intervals between.

Influence of Sex.—The incidence of acute rheumatism upon the sexes in childhood differs remarkably from that in the period of maturity.

Taking all ages of life together it falls nearly equally on males and females, somewhat more heavily on the former. In childhood, however, the case is reversed, and the disease is most common in girls. The proportions, however, shew curious variations.

According to the statistics yielded by the reports of the Collective Investigation Committee, in the first period of from 1 to 5 years of age boys preponderate in the proportion of 5 to 1. In the next quinquennial period, from 6 to 10 years, they become nearly equal, in the proportion of 15 to 14. In the next period of 11 to 15 years there comes a remarkable change; the proportion is suddenly reversed, the girls suffering in the proportion of nearly 2 to 1. This explains in some degree, probably, the greater prevalence of chorea in girls about this period of life. After the age of 15 the greater liability of females declines up to 20 years, so that at the close of this period males preponderate.

Another point with regard to acute rheumatism, which comes out with especial clearness and force in the case of children, is the potent influence of hereditary disposition. The statistical evidence recorded in this respect is unsatisfactory and, indeed, obviously defective. The results shew great discrepancy, owing to differences in the thoroughness of the inquiry, the nature of the evidence allowed, and the class of patient from which it is drawn. Most of the material was obtained from hospital patients of the poorer class, who generally know little of their relations, or of the diseases from which they suffer; and the inquiry was usually based upon the history of articular affection alone. More trustworthy data can be obtained from private cases; parents of the better class know a good deal about the diseases of their own children and of immediate blood-relations. Statistics from private cases of acute rheumatism under my own observation give a proportion of 70 per cent in which there is a definite family history of the same affection in near blood-relations. Many examples have been recorded which shew a remarkable family incidence, the individual cases often occurring apart, and not, therefore, attributable to locality or infection. The most significant point of all is the power which double inheritance appears to exercise in intensifying the tendency to the disease. When acute rheumatism prevails in the families of both parents, not only is the liability to the disease increased, but its severity and persistence are increased also. The most inveterate and fatal cases which have come under my observation have had this double strain; and similar examples have been recorded by Dr. Goodhart, Dr. Garrod, and others.

As the phenomena of acute rheumatism in childhood are more varied and extensive than those met with in later life, so each in turn presents points of difference from the same condition in adults, and requires detailed and individual consideration.

Arthritis.—It has already been stated that in childhood the articular affection is usually slight, indeed it is less extreme in every way than in the case of adults; there is less swelling and tenderness, less pain and

fever. It is a comparatively rare thing to see a young child lying motionless, bound hand and foot, and not daring to move or turn in bed for fear of pain—a condition so characteristic of the disease in older people. There is often merely a little pain, stiffness and tenderness, without perceptible swelling, limited perhaps to a single joint or set of joints. Sometimes the affection of the fibrous tissues is extra-articular, confined to the tendons or the fascia in the neighbourhood of the joint, and analogous to the stiff neck which sometimes indeed is the only sign of rheumatism. The tendons of the hamstring muscles under the knee, for example, may be attacked alone, causing stiffness and pain on movement; a child thus affected walks on the tips of the toes, with knees bent to avoid tension of the sinews—a very characteristic sign. Such minor attacks are apt to be overlooked altogether, or regarded as simple feverish attacks, not severe enough to require medical aid, and soon forgotten. Yet, slight as the articular signs may be, they are frequently accompanied by a subacute endocarditis or pericarditis, leading eventually to grave heart lesions. These considerations afford the key to many instances of unexplained heart disease and of chorea.

The slight arthritis of acute rheumatism in childhood often assumes a misleading aspect, so that it may be difficult to distinguish it from other ailments involving pain and tenderness of limbs and joints. Its early recognition is, however, of the first importance, since, as previously stated, an insidious and deadly endocarditis or pericarditis may be at work concurrently with it. The affection of the hamstring muscles, with walking on the toes, and apparent inability to put down the heel, has been mistaken for incipient talipes, and treated accordingly. Similarly, the disinclination to walk has been attributed to paresis and loss of power to do so. Conversely, other morbid conditions are often mistaken for articular rheumatism. In my experience the mistake is most frequently made in infantile scurvy. The swelling, immobility, and extreme tenderness of the limbs, accompanied often by slight transient pyrexia, at first sight simulate articular rheumatism very closely. Scurvy, however, may usually be distinguished by the periosteal position of the swelling, which, moreover, is almost invariably limited to the shafts of the long bones. In one of my own cases there was periosteal swelling over the malar bone; and in another a swelling of the periosteum of the lower part of the tibia appeared to extend to the joint structures. Such cases, however, are rare exceptions. Other diagnostic points are the existence of spongy gums, subcutaneous and other hæmorrhages, hæmaturia or albuminuria; although these are not always present. Moreover, infantile scurvy is limited to the bottle-feeding period of infancy, that is, to the first eighteen months or two years of life, when articular rheumatism is almost unknown.

Infantile palsy (acute anterior polio-myelitis) in its early stage, when there is often considerable hyperæsthesia, is another affection liable to be confounded with acute rheumatism. The chief points of distinction are that in infantile paralysis there is extreme flaccidity of muscle; the

affected limbs are limp and fall loosely down with drooping of the toes, while the tenderness is found to be diffused and general, not confined to joints and tendons. Later the disappearance of faradic contractility and tendon-reflex is decisive. Another condition liable to be mistaken for slight rheumatic arthritis is syphilitic disease of the ends of the long bones. In this there is tenderness and swelling from accompanying periostitis, and there may even be some articular inflammation, with pain on movement. It is to be distinguished from true rheumatic affection by the presence of other signs of congenital syphilis, or by the history; but the most distinctive feature is the age at which it occurs, namely, in the first few months after birth, when rheumatism is practically unknown. I have never met with a case of acute rheumatism in early infancy, although rare instances have been recorded by Senator, Henoch, and others. Possibly these may have been examples of syphilitic affection, or of infantile scurvy, a disease at that time hardly recognised. The swelling of the wrists in tetany, the arthritic hæmorrhages of hæmophilia, the joint trouble of tuberculous disease, the arthritis of pyæmia, and acute osteomyelitis, are also conditions met with in children which are liable to be mistaken for rheumatic arthritis.

The inflammation of the joint-structures in children being slight, certain symptoms especially associated with it are slight also. The profuse acid perspirations, so marked in the acute rheumatism of grown persons, are not common in children. Pyrexia, again, is rarely high, and this is the more remarkable as in children the temperature tends to rise from slight causes. In rheumatism, so eminently pyrexial a disease as far as adults are concerned, the temperature in the case of children seldom rises above 101° or 102° F.; degrees of 103°, 104° are comparatively uncommon, and usually of short duration.

Hyperpyrexia, which occurs now and again in the acute rheumatism of adults and is so grave and often uncontrollable, is at least extremely rare in childhood. I have never seen an instance of excessive or fatal hyperpyrexia in a child, nor any case in which the temperature has shewn a persistent tendency to run up rapidly beyond control to a fatal height. The earliest age I can find recorded at which fatal hyperpyrexia occurred is thirteen.

Abdominal Pains.—Pains in the abdomen have been noted in connexion with acute rheumatism by Drs. Still, Poynton, and others, and more recently by Dr. V. Pearson, who describes them as short, sharp, paroxysmal—radiating from the costal cartilages on either side towards the umbilicus or the epigastrium—they last for a few minutes only, but recur from time to time, and appear to be brought on usually by muscular exertion or by excitement. They have not been observed to be associated with stomach or bowel disorder or with any particular phase or degree of the various other manifestations of acute rheumatism. Their importance depends upon their value as possible indications of the imminence of more definite and serious symptoms of a rheumatic invasion.

Anæmia.—The effect of acute rheumatism in producing anæmia is well known, and in children this is even more noticeable than in adults. When the rheumatic state is actively manifested in children anæmia proceeds apace, and hæmic cardiac murmurs are frequent. With the single exception of that of diphtheria there is no organic poison which causes such rapid blanching as that of rheumatism.

Cardiac Inflammations. — In children, as Sturges pointed out, more than in adults, the heart is apt to suffer in all its structures at the same time; endocarditis, pericarditis, and myocarditis are liable to occur together, and the carditis to be general. This, however, chiefly arises towards the close of fatal cases, when rheumatic attacks recur, and endocarditis has already given rise to valvular lesions. Then pericarditis, accompanied by myocarditis, is usually added to the original endocardial inflammation. As a rule, however, endocarditis occurs first and alone.

Endocarditis occurs acutely in the course of articular rheumatism in children as it does in adults. More often, however, it comes on in a subacute, insidious, progressive form, which is characteristic of the disease in childhood, when the arthritis may be slight, or at the time even inappreciable. Endocarditis may indeed appear at any stage of the rheumatic procession of events, early or late, entirely alone or in combination with arthritis or chorea, or nodules, or pericarditis, or with any or all of these combined. Usually it comes early in the series and recurs, wherein it stands in contrast with pericarditis, which is apt to appear towards the close. Most often it arises in connexion with slight arthritis or with chorea; and, not seldom, valvular lesion, due to antecedent endocarditis, is discovered already established when the first joint affections or chorea attract attention and lead to examination of the condition of the heart.

As might be expected from the law that in children endocarditis arises in connexion with slight manifestations of the other forms of acute rheumatism, or even apart from them, inflammation of the endocardial valve-structures is nearly twice as common in the case of children as in that of adults.

It has been stated that endocarditis is liable to come on insidiously, without its existence being known or suspected until some other rheumatic manifestation leads to examination of the heart, and to the discovery that valvular mischief is already established. Even when it arises in the course of an attack of articular rheumatism, and is discovered at the outset, the signs of it are vague, slight, and slowly developed; some quickening of the pulse, with an excited, uneven, irregular action of the heart, and changes in the cardiac sounds afford the earliest indications. The most common of the latter is the soft, blowing, systolic murmur at the apex with accentuation of the pulmonary second sound, which indicates a commencing mitral leakage, due to the thickening and rigidity of the flaps and chordæ which lead to imperfect closure of the valve.

Another early sign is reduplication of the second sound, not at the

base but at the apex; it is probably due to a retarded opening of the mitral gate resulting from rigidity caused by inflammatory thickening. With this there are sometimes—not usually at the outset but after a time —a soft, blowing, diastolic murmur after the later of the two second sounds, and an accentuation of the first sound, signs of changes which gradually lead to stenosis and, long afterwards, to the development of a true presystolic rumble. Although, as a rule, endocarditis in children sets in and progresses insidiously and slowly, giving little outward sign of its existence, and often recurring frequently in subacute form, occasionally it proceeds with great rapidity. In such cases there is more fever and constitutional disturbance, and the valvular inflammation progresses quickly; so that a murmur which began as a soft, gentle, blowing sound, the very existence of which appeared doubtful when first detected, may (according to my observation) increase to a loud musical bruit in the course of a single week. The concurrent eruption of subcutaneous nodules is always a grave sign indicative of serious and generally persistent or recurrent valvulitis, often accompanied by pericarditis also. Rheumatic endocarditis in children, as in adults, may attack either the mitral, aortic, or tricuspid valves; yet the first is by far the most common event, and mitral regurgitation the most usual lesion; nevertheless mitral stenosis is more common than is generally believed. Mitral stenosis, indeed, is the special product of the subacute, slow, recurrent course which is so characteristic of endocarditis in childhood, and it is in the time of childhood that the mischief usually begins. The reduplication of the second sound at the apex, or the slight accentuation of the first, which are the early signs of it, escape notice. These changes are the results of the stiffening of the valve-flaps from inflammatory thickening, which produces virtual stenosis; although there may be no fixed constriction of the orifice. The loud, vibrating, prolonged, presystolic bruit and slapping first sound are not common in childhood; they do not usually appear until some years later, when the disease is advanced, and the mitral orifice has become permanently narrowed. Hence the rarity of a pronounced presystolic murmur in early childhood, and its discovery with such startling frequency about the age of puberty. Thus also, no doubt, arose the error of regarding mitral stenosis as usually non-rheumatic in origin.

Infective endocarditis is the most rare sequel to the rheumatism of children, since it is most often met with in subjects broken down by drink and disease. Two cases only have come under my own observation, one in a girl of eight years old and the second in a boy of ten. Other instances have, however, been noted, notably one in a girl aged nine years, recorded by Dr. Poynton (51).

Pericarditis may arise at any step in the rheumatic series; first or last; alone, or combined with any one or more of the other manifestations, such as endocarditis, arthritis, the evolution of nodules, or chorea. Most often, however, it comes late, in association with recurrent endocarditis, when the heart is already hypertrophied and dilated. So that,

as Sturges pointed out, it is almost always found post-mortem in the fatal heart disease of children. As in the case of endocarditis, pericarditis in children is usually subacute, chronic, recurrent. It may occur acutely, as in the rheumatism of adults, with rapid exudation and effusion of fluid, pericardial distension and distress, but this course is exceptional; as a rule it proceeds insidiously, with slight symptoms, although these are more distinct and recognisable than those of valvular inflammation.

The first appreciable physical sign of subacute pericarditis is usually a slight pericardial rub, which may be constant, or intermittent, or may cease altogether. The child is seen to be restless and uncomfortable; and, if old enough, complains of pain in the præcordial region, which is generally a little tender on firm pressure. The pulse quickens to 120 or 130, out of proportion to the temperature, which is usually but slightly raised, say to 99° or 100° or 101° F. This quickened pulse-rate, without adequate rise of temperature, is very characteristic of the subacute pericarditis of early life. Anæmia increases in a marked degree; chorea if present becomes aggravated, or curious emotional attacks come on, in which the child is moved to tears or laughter by a word. With these signs a mitral murmur perhaps appears, or an existing murmur grows louder and rougher; subcutaneous nodules also often arise on the elbows and knees, or on the ankles or occiput; these are always suggestive of a grave implication of the fibrous structures of the heart. The pericardial rub, if it has ceased, reappears after an interval; or the extent of cardiac dulness may shew the variations due to a fluctuating amount of effusion; the effusion, however, is never large, and usually is quickly reabsorbed.

Further—the most significant indication of all—although the physical signs of friction and effusion subside, due probably to the formation of pericardial adhesions, the rapid action of the heart, in spite of digitalis, belladonna, ergot, or strophanthus, continues unchanged. The area of cardiac dulness increases, and there is muffling of the sounds over the mid-cardiac region—probably not due to effusion, but to the increased size of the heart and thickening of the pericardium. Enfeeblement, anæmia, emaciation proceed apace: the pulse grows weaker; and so after weeks or months the patient sinks from heart-failure and exhaustion, without dropsy or marked dyspnœa: or the symptoms may subside to recur at intervals, and the course of the disease may thus extend over years instead of months.

Occasionally endocarditis and pericarditis, together with myocarditis, run an acute course, dilirium supervenes, respiratory distress becomes great; vomiting, which is often obstinate and persistent, not infrequently sets in, and prostration becomes extreme. Such symptoms always indicate a condition of great danger. These cases as a rule arise when pericarditis occurs late, when the heart is already seriously damaged by previous attacks of endo- or pericarditis, and the secondary changes of dilatation and hypertrophy, and perhaps adherent pericardium, have already advanced to a marked extent.

Pericardial Fibrosis.—The results of the chronic recurrent pericarditis of childhood are serious enough. In many instances the pericardium becomes greatly thickened, and its two surfaces so closely adherent that, when examined post-mortem, all sign of the space between them is found to have disappeared, and the heart is enclosed in a tightly fitting sac of fibrous tissue, sometimes as much as an eighth of an inch in thickness. The chronic inflammatory process spreads now and again from the pericardial sac to the tissues of the pleura and adjacent mediastinum, so that these become matted together in a thick fibrous mass—an indurative mediastino-pericarditis. This is indicated clinically by ascending dulness along the middle and upper sternum, and increased respiratory and cardiac distress. In certain cases fibrous growths cause pressure upon the great vessels at the base of the heart; such pressure is most operative upon the veins, leading to hepatic engorgement, cirrhosis with ascites, imperfect filling of the pulmonary arteries, cyanosis, dyspnœa, and general dropsy. These cases of mediastino-pericardial fibrosis are rare; but several have come under my own observation, and others have been recorded.

Another occasional result of this chronic fibrous pericarditis of childhood is worthy of notice. The tight, strangling grip of the inelastic fibrous sac not only interferes with the contraction and dilatation of the cardiac chambers, and thus causes grave embarrassment of the heart's mechanism, but it interferes also with the progressive development of the organ in childhood, so that it fails to grow in proportion to the rest of the body, and general dropsy eventually follows as the result of imperfect cardiac power. Cases of the kind are recorded by Watson and Bouillaud, and several have come under my own observation.

Myocarditis.—With pericarditis, and probably to some extent with endocarditis, there is always some degree of inflammation of the muscle lying beneath; or rather perhaps of the intermuscular connective tissue, extending to the muscle-fibres themselves. These are found after death to be swollen, blurred in outline, with numerous nuclei, and proliferation of the interstitial fibrous tissue. In some cases in which myocardial weakness has been disproportionate to the valvular lesions, extensive fatty changes have been found in the muscle-fibres, pointing to a peculiarly toxic effect of the rheumatism upon the myocardium.

In old-standing cases of chronic pericarditis, with adherent pericardium, there is marked increase of interstitial fibrosis, and the striæ of the muscle-fibres become indistinct or are altogether lost. These changes of interstitial fibrosis and degeneration of muscle-fibre account in part for the cardiac failure which is so conspicuous in the last stage of heart disease in children.

Hypertrophy and Dilatation.—All that need be said about these secondary changes is that, other things being equal, these changes proceed more rapidly in the case of children than in adults. In accordance with the general law that in early life the tissues respond more quickly and readily to stimulation, and grow more vigorously than after maturity,

FIG. 8.—Acute rheumatism. Grave form, with numerous large nodules. Fatal.

W. S., æt. 4 years and 3 months. (Hospital for Sick Children, Great Ormond Street. December 10, 1887. Under the care of Dr. Cheadle.) Rheumatic nodules, erythema marginatum, chorea, double mitral murmur, arthritis.

hypertrophy develops faster, and dilatation is more rapid; probably because the tissues are softer and more yielding.

Dropsy and other Complications.—The ready development of hypertrophy, in response to increased strain, renders compensation exceptionally complete at first, and probably accounts for another special feature of the rheumatic heart affections of children, namely, that the common complications of disease of the heart in adults, such as pulmonary apoplexy, enlargement of the liver and extreme dropsy, are rare in the younger children. It is an unusual thing to see a little child blue, turgid, and waterlogged—a sight so sadly frequent in the last stage of valvular disease in adults. In addition to effectiveness of compensation, however, there is another reason for this immunity; children with severe heart disease usually die from other causes before the stage of grave tricuspid leakage is reached—from anæmia, wasting, asthenia, rather than from direct obstruction to the mechanism of the circulation; unless it be in the case of the strangling grip of pericardial fibrosis and adhesion.

Subcutaneous tendinous Nodules.—Another exceptional and special feature of acute rheumatism in children is the development of subcutaneous nodular growths of fibrous tissue. Not uncommon in early life, they are comparatively rare phenomena in the case of adults. They may appear in connexion with any of the other phases of rheumatism, but are mostly associated with endocarditis and pericarditis, and in this relation are of serious import. They appear to have been first noted by Hillier, and subsequently by Meynet and others; but their comparative frequency and clinical significance were first pointed out by Sir Thomas Barlow and Dr. Warner. The nodules lie under the skin in connexion with fascia or tendons, that is, in relation with fibrous tissue; and similar nodular proliferations have been found in the periosteum, and even in the pericardium. They vary in size from that of a hemp-seed to that of an almond, or are even larger; when small they may not become visible until the skin is drawn tightly over them, although easily detected by the touch. They are not tender except slightly so in rare instances; nor is there redness of skin over them unless it arise casually from friction or pressure. There may be but one of these nodules; but three or four are usually found; sometimes, indeed, the number is large, as many as twenty or thirty. In one extreme instance of an intense rheumatic state within my observation, it was calculated that 200 were present at one time. These fibrous nodules grow to a perceptible size in the course of a few days; but, when large, they take a considerable time to attain to their full dimensions. Their duration varies from a few days to several months — the minimum period recorded being three days, and the maximum five months. When examined microscopically in the early stage they are found to be due to a local exudation from the minute blood-vessels, with swelling and even necrosis of the tissue in the centre of this change. Drs. Poynton and Paine have demonstrated the presence of diplococci in these nodules in this early condition of formation. Later, they are seen to consist of nuclear growth in all stages of transformation

into fibrous tissue—a proliferation analogous to that which is seen in the interstitial framework of the liver, or of the kidney, in cirrhosis. The connexion of these nodules with rheumatism and rheumatoid arthritis is almost absolute. In very rare instances their appearance has been re-

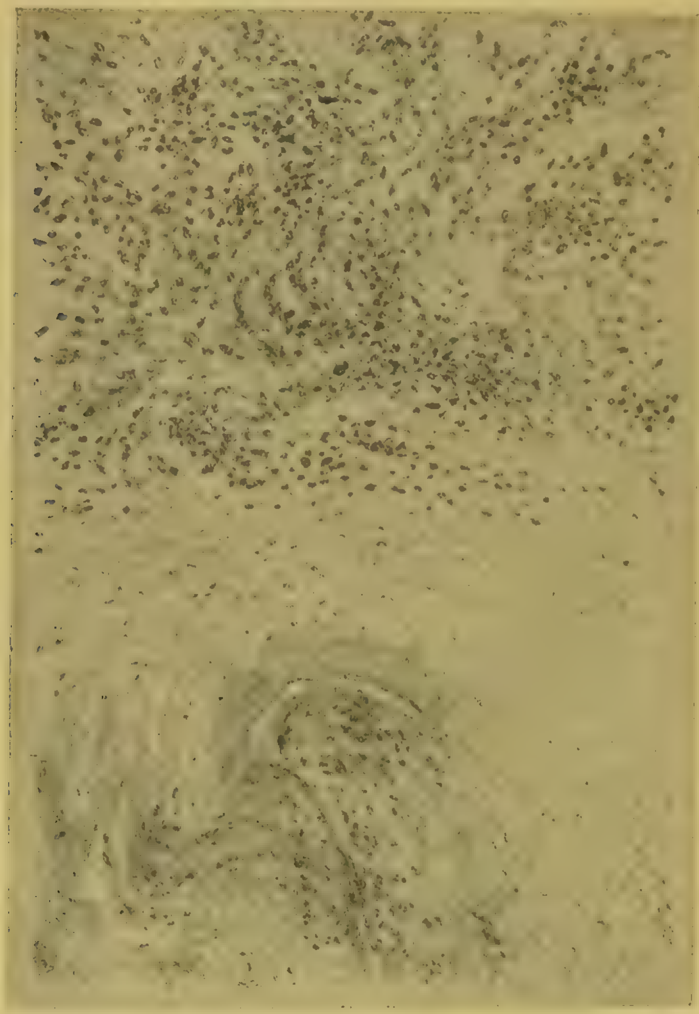

FIG. 9.—Section of subcutaneous tendinous nodule in acute rheumatism, shewing active proliferation and cell-infiltration of fibrous tissue.

John T., æt. 7½ years. (Hospital for Sick Children, Great Ormond Street. August 1888.) Chorea, arthritis, endocarditis, pleurisy, nodules, pericarditis.

corded after influenza, and in syphilis after the administration of iodides: the nature of the latter is, however, doubtful.

General experience has confirmed the views originally expressed by Sir T. Barlow and Dr. Warner as to the grave significance of these fibrous outgrowths. They indicate concurrent and usually progressive cardiac disease; that a similar process of inflammatory change and proliferation

is going on in the fibrous tissues of the cardiac valves or pericardium, or in both. In the acute rheumatism of children, when the nodules are many and large, they have an ominous association with progressive endocarditis and pericarditis of the most serious kind; they indicate

FIG. 10.—Section of aortic valve in infective endocarditis in a child, shewing proliferation and cell-infiltration of subendothelial fibrous tissue, similar to that of the subcutaneous nodule shewn in Fig. 9.

grave danger, a carditis which is uncontrollable, and advances almost inevitably to a fatal ending.

Eruptions associated with Acute Rheumatism.—*The exudative erythemas and purpura rheumatica* are far more frequently associated with the rheumatic state in the case of children than of adults. They may appear at any stage of the rheumatic series, but generally arise in

connexion with active disturbance of other kinds, such as arthritis; and not infrequently with the endocarditis and pericarditis of the more serious cases.

The erythemas occur chiefly in children, in marginate, papular, or urticarious forms; erythema nodosum is less often concurrently associated with other phases of rheumatism than the rest. Its appearance, however, from time to time in immediate connexion with a rheumatic outburst seems to stamp it as one of the rheumatic phenomena, and it is occasionally met with in childhood.

Purpura rheumatica is an eruption or hæmorrhagic condition which occurs almost exclusively in childhood. Some cases of rheumatic purpura are clearly extreme instances of erythema, in which hæmorrhagic extravasations are unusually marked. Others, again, are possibly instances of simple purpura or of hæmophilia, in which there is oftentimes tenderness and swelling of adjacent joints. There is, however, a purpura closely associated with acute rheumatism, occurring concurrently with general arthritis, or in subjects who have suffered from articular rheumatism. In the latter case it has an arthritis of its own, the joints in proximity to the eruption—especially the feet and ankles when it appears in the legs—being swollen, tender, and painful, although there may be no rise of temperature. In a few rare instances this condition is accompanied by hæmaturia.

Tonsillitis is another rheumatic phase which is perhaps somewhat more common in children than in adults; but it shews no special features in early life.

Pleurisy, pneumonia, bronchitis, and other inflammatory conditions of minor importance occur occasionally in the course of rheumatism in childnood as in later life, but they have no distinctive characters at the early period which call for remark.

Chorea.—One of the most interesting properties of acute rheumatism in childhood, and one almost entirely confined to that period of life, is its connexion with chorea. Genuine chorea, apart from mere grimacing (which is a disturbance of the second dentition, and not in any way connected with rheumatism), is very closely associated with the rheumatic state. It appears not only in direct connexion with acute rheumatism of the joints, but with endocarditis also, with pericarditis, with erythema multiforme and nodosum, and, above all, with that especial rheumatic sign the evolution of subcutaneous nodules. Chorea may appear in relation to one or more of these; and when it occurs alone, apart from any other rheumatic manifestations at the moment, is often followed at an interval by arthritis, or by other rheumatic manifestations. It is especially liable to occur, even when alone, in members of families in which rheumatism is rife: one individual may have articular rheumatism, another endocarditis, another chorea. The chain of evidence in favour of the rheumatic nature of chorea in the case of children is remarkable. The identification of the diplococcus of rheumatism in cases of chorea recently by Drs. Poynton and Paine seems to me conclusive as to the rheumatic relation. It is

impossible to state it in detail here, but it may be affirmed that the presumption is strongly in favour of the view that, in the great majority of cases at all events, chorea is of rheumatic origin. We may almost certainly say that the endocarditis and pericarditis of chorea are invariably rheumatic in nature and origin. (*Vide* art. "Chorea," vol. vii.)

In relation to this may be mentioned the curious association of the neurotic groundwork of chorea with the rheumatic taint. According to my own observation, the rheumatic child in a family is the nervous child of the family; but no distinct association with specific nervous family disease can be satisfactorily traced.

Scarlatinal Rheumatism.—The articular affection which appears now and again in the course of scarlatina, and which can in no way be distinguished from that of acute rheumatism, is naturally a form met with chiefly in childhood. It is often accompanied by endocarditis or pericarditis, sometimes by chorea; and subcutaneous nodules have more than once been observed in the course of an attack.

This scarlatinal rheumatism usually arises early; it has been observed on the third day, but occurs most frequently about the end of the first week. And it is noteworthy that the especial liability to acute articular rheumatism which obtains in girls extends also to the scarlatinal form. (*Vide* p. 456.)

Rheumatoid arthritis occurs occasionally in childhood as a sequel of acute rheumatism, sometimes in its most severe and intractable form. Such cases are, however, rare, and present no distinctive characters. (*Vide* vol. iii.)

Prognosis.—The prognosis of acute rheumatism is far more serious in the case of children than in that of adults. This results chiefly from the greater tendency to endocarditis and pericarditis, the proclivity to which may be roughly stated to be inversely as the age of the patient. The danger from this source is no doubt aggravated by the fact that in many cases the first stages of heart disorder are apt to be overlooked, owing in some cases to the slight character of the articular affection which accompanies it, and to its entire absence in others. Thus the cardiac inflammation runs on unchecked by the palliation of rest and appropriate treatment. A further source of increased peril in childhood lies in the remarkable tendency of the disease at this period to recur, so that the heart is liable to become fatally injured by repeated attacks of endocarditis and pericarditis.

In mild cases, no doubt, the rapid growth of muscle favours quick and complete compensation; but in severe cases the ready dilatation of the young tissue more than counterbalances the rapidity of its remedial growth.

Treatment.—The affection of the joints, with its accompanying pain and tenderness, being in the case of children almost invariably of small intensity, and not the cause of any great distress, the pyrexia also being in most instances moderate—all symptoms, in fact, both articular and constitutional, being subdued and subacute—anything like active treatment

by full doses of salicylate of soda, so effective in the case of adults, is rarely required. Not infrequently, indeed, it does great harm by its depressing effect, for children bear severe and drastic measures badly. In place of salicylate of soda, salicin may be given in doses of from 5 to 20 grains, or quinine in doses of 1 to 3 grains, every four to six hours. With this an alkali should be combined, such as citrate of soda or of potash, in doses of 5 to 20 grains according to age.

The general evidence of statistics of the Collective Investigation Committee is in favour of the conclusion of the late Dr. Fuller and of Dr. Dickinson, that cardiac inflammation is less frequent and less pronounced under full alkaline treatment than under any other. In the case of children this is especially important, for the chief interest and danger centres in the cardiac implication and its results, and not upon the pain and distress of articular troubles. The one great object of treatment should be to diminish this danger as far as possible.

The first and most important point is to guard against an insidious or masked attack of endocarditis or pericarditis. It has been shewn that this may accompany the slightest articular affection, or be associated with chorea, or an exudative erythema, or an eruption of subcutaneous nodules; or again it may arise apart from any known rheumatic phase with an indeterminate febrile attack of apparent insignificance. It is essential, therefore, to examine the condition of the heart carefully, not only in every case where there is the slightest articular or other known rheumatic condition, such as a stiff neck, or a stiff knee, wrist, or ankle, in chorea, in tonsillitis, in an evolution of nodules, but also in every pyrexial condition of any kind arising in a child. Whenever there is a suspicion of rheumatic inflammation, it is wise to enforce absolute rest in bed, even if no cardiac disturbance be perceptible. Complete physical repose and external warmth are of vital importance. Sibson found that a much larger proportion of patients—more than two to one—treated by rest escaped permanent heart mischief as compared with those allowed free action.

Cases of rheumatism in children are as a rule treated far too lightly. A little timely care, the avoidance of fresh chill, and of excitement of heart or strain of its muscle, may make all the difference in the degree of cardiac mischief. In every case of acute rheumatism in a child, however slight the joint affection, or pain, or pyrexia, or signs of cardiac inflammation may be, the patient should be kept at rest in bed for a fortnight at least after all pain and rise of temperature or cardiac excitability, as evidenced by acceleration or irregularity of pulse have completely disappeared. If endocarditis or pericarditis have been severe the period of rest should be extended to a month or more, and the patient debarred from all active physical exertion for many months in addition.

In cases of active pericarditis, accompanied by pain, tenderness, and distress, the application of an ice-bag, as recommended by Dr. Lees, is usually grateful, relieves pain, and appears to exercise a favourable influence on the inflammatory process. In cases of extreme severity one or two leeches may be applied to the præcordia, but anything like profuse

extraction of blood by leeches is injurious. Children bear loss of blood ill. Blisters are, I am convinced, useless to allay the cardiac inflammation, and although valuable agents in relieving pericardial serous effusion this is so exceptional in the case of children that the occasion for this application occurs most rarely. In cases of persistent, recurrent, intractable endocarditis and pericarditis, which form such sad and especial features of the acute rheumatism of children, digitalis, strophanthus, strychnine, and opium are the drugs of most service. The latter is best given in the form of nepenthe, and in frequent small doses of half a drop to five drops, according to age. More than any other remedy it relieves distress, lessens dyspnœa, and procures sleep. If given with care and discretion no harmful effect need be anticipated. Alcoholic stimulants help by their sedative influence as well as by increasing cardiac power. When the embarrassed heart, by feeble beat, small irregular pulse, and tendency to syncope, shews signs of failure, hypodermic injections of liquor strychninæ in doses of $\frac{1}{8}$ of a minim to 1 minim or more, according to age, combined with 5 to 10 drops of brandy, and given every four to six hours, are the most powerful means of sustaining the failing circulation. Or $\frac{1}{2}$ a minim to 3 minims of tinct. of digitalis may be administered in the same way. In the case of children under seven years of age, however, these remedies should not be administered hypodermically, except in conditions of extreme and urgent danger, and then with the greatest caution and watchfulness.

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INFECTIVE DISEASES OF DOUBTFUL NATURE

COMMUNICABLE FROM ANIMALS TO MAN

VACCINIA.

Pathology of Vaccinia.

Vaccination as a Branch of Preventive Medicine.

FOOT-AND-MOUTH DISEASE.

HYDROPHOBIA.

VACCINIA IN MAN—A CLINICAL STUDY[1]

By T. D. Acland, M.D.

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[1] In the following pages frequent reference is made to the various reports and appendices issued by the Royal Commission on Vaccination between 1889 and 1896. To save repetition these volumes are referred to as R.C.V. Final Report ; R.C.V. Appendix ix., etc. ; the latter contains the papers relating to cases in which "injury or death was alleged or suggested to have been caused by vaccination, or to have been connected with it." Of these cases 205 were inquired into by the medical staff of the Local Government Board, and the abstracts of these reports were prepared for the Commission by Dr. Coupland and myself. Besides these, 421 additional cases were brought to the notice of the Commission ; and most of them were investigated by Dr. (now Sir Thomas) Barlow, Dr. Coupland, Dr. Luff, and myself. These inquiries extended over a period of seven and a half years ; that is, from November 1888 to April 1896. The writer is greatly indebted to those who, often at some personal inconvenience, have given him assistance in investigations which were, in some instances, necessarily prolonged ; and he wishes to take this opportunity of acknowledging the help which has been given him, both by the supporters and opponents of vaccination, without which help many of the investigations would have been impossible.

PART I

VACCINIA NORMAL AND ABNORMAL

Introduction.—Vaccinia in man is a communicable disorder arising, except in very rare instances, from the accidental or intentional inoculation of an individual with vaccine lymph. The disease is probably due to a specific contagium (9A) (*vide* p. 754). It has definite periods of incubation, evolution, and decline; and is characterised by an eruption at the point of inoculation, which eruption has certain well-recognised features.

It is improbable that any more precise definition of vaccinia will be possible until its origin and affinities are more fully determined than at present. Nor is there anything surprising in this, since similar general definitions have to suffice for all the acute exanthems—such as small-pox and scarlet fever—the recognition of which depends rather on a given train of symptoms, than on a precise knowledge of their causation.

The expression "vaccinia in man" is taken to denote the sum of the results produced by the inoculation of uncontaminated vaccine lymph, as generally practised throughout the United Kingdom.

The course of vaccinia may be normal or abnormal. It may be called normal when the events, subsequent to vaccination, pursue a certain definite and recognised sequence. The gradations, however, between normal and abnormal vaccination are insensible, and no hard-and-fast line can be

drawn between them; although between the cases which occur at either end of the scale there are wide and striking differences.

Normal vaccination results from the inoculation of a healthy individual with vaccine lymph uncontaminated with extraneous micro-organisms, or other organised or unorganised products, which, although not infrequently present, are not, so far as is known, in any way essential to the process of vaccination or to the production of immunity from small-pox. Calf-lymph treated with glycerin or chloroform is practically free from all extraneous organisms, and even if in some few cases spores escape destruction by these methods, the healthy tissues of the vaccinated individual, in the vast majority of cases, offer sufficient resistance to obviate any ill results (44 and Copeman, 9A, p. 153 *et seq.*). The power of resistance, however, is not the same in all cases, and this may probably explain why occasionally one or more individuals of a series inoculated with the same lymph, develop inflammatory symptoms—such as cellulitis, abscess, or even possibly erysipelas—whilst in others of the same series vaccination pursues a normal course.

It is sometimes urged against vaccination, that it is impossible by examination of the lymph to determine with certainty what results will be obtained. This objection has little weight, since although no microscopical examination of lymph in bulk will reveal pathogenetic or pyogenetic organisms, and it is doubtful whether lymph, collected in the ordinary way, does not always contain blood-corpuscles, calf-lymph collected and prepared by recent methods is almost entirely free from these possible sources of danger,[1] and, moreover, experience shews that lymph taken from normal vesicles in healthy individuals produces certain definite results in healthy and properly cared for infants, even when the vaccination is performed direct from arm to arm without any previous treatment of the lymph. On the other hand, no selection of lymph will remove dangers which arise from the method of vaccination, the circumstances or condition of the child, or the improper treatment of the vesicles: all which factors are found to be far more productive of untoward results than any defect in the quality of the lymph itself.

Normal vaccination.—Under favourable conditions vaccination is followed by local manifestations and general symptoms which, within certain limits, vary according to the strength of the virus used, and the

[1] Although calf-lymph treated with glycerin or chloroform, and prepared in properly appointed laboratories under skilled superintendents, is largely used in England and Wales, and is supplied to all Public Vaccinators, it is supplied to them *only*. Private practitioners are obliged to depend upon supplies of lymph from trade sources. It is almost incredible that a nation which is so particular that *margarin* should not be labelled *butter*, permits any preparation to be imported and sold as vaccine lymph without requiring a guarantee as to its source, origin, or nature. It cannot be unreasonable that all individuals vaccinated in compliance with the law should have the right to the use of lymph prepared by the most scientific methods in laboratories kept up at the expense of the nation, whether they are vaccinated by a private practitioner or by the Public Vaccinator. As long as the present state of things continues there can be no certainty that vaccinations performed by others than the Public Vaccinator at the public expense are done with lymph which is either efficient or prepared with all the safeguards which are universally admitted to be necessary (cf. 9A, pp. 153 and 189, and R.C.V. App. ix. Section 418).

peculiarities and circumstances of the individual. The local manifestations are so well known as to need but the briefest mention.

Period of Incubation.—In most cases the immediate effect of the operation is nothing more than that which results from a scratch; but in some children of unusual susceptibility, there is immediate evidence of some slight traumatic reaction, such as swelling and redness of the part, which in the course of a few hours entirely subsides until the end of the incubation-period. This stage lasts as a rule for about three days.

Period of Eruption.—On the 3rd or 4th day, pale red papules develop at the points of inoculation, which, in the course of the next five days, develop into compound vesicles with clear contents, and later, about the 10th day, into pustules; the lymph becoming more and more opaque owing to the multiplication of the cellular elements which it contains. The vesicles are at first fully distended and plump; as they approach maturity they become umbilicated, the centre begins to dry, and a scab is formed which increases towards the periphery, and eventually covers the whole pock. Between the 14th and 20th days the scab falls off, leaving a scar which, dusky red at first, gradually, after some months, becomes white and pitted (foveated). The amount of pitting as a rule varies inversely as the amount of inflammation at or round the seat of inoculation (for abnormal conditions of the scar, see p. 671).

About the 5th day, when the vesicles are beginning to form, a faint blush appears round them. This "areola" becomes more intense about the 9th or 10th day, gradually subsiding with the drying-up of the pocks, which begins about the 11th day. The areola extends from $\frac{1}{4}$ inch to 2 inches round the pocks, the tissues becoming indurated and painful in proportion to the severity of the inflammation. This areola, formerly supposed to be an important part of vaccination, varies greatly in intensity, and probably is largely dependent on the kind of lymph used and the method of preserving it. With glycerinated calf-lymph it tends to be very slight. (The alleged relations of the areola to erysipelas will be found discussed on p. 699.)

With the retrogression of the pock and the subsidence of the areola the local phenomena of a normal vaccination are at an end.

Variations in the development of the vesicles.—Although in ordinary circumstances the development of the vaccine pocks proceeds in the manner sketched above, there are frequent departures from the normal course, most of which are of little or no importance; many depend on the condition of the vaccinee and his circumstances, some on causes quite independent of vaccination and easily preventable. No useful purpose would be served by giving details of all the variations from a definitely regular development of the vesicles; but the following table indicates the kind of irregularities which are met with from time to time:—

TABLE shewing variations in the development of vaccine pocks.

a. Variations in number . . .	Supernumerary pocks. Confluent pocks round points of inoculation. Generalised vaccinia.
b. Variations in size	Due to coalescence of vaccination-vesicles. Due to extension of original vesicles by coalescence of surrounding secondary pocks.
c. Variations in contents . . .	Serous. Purulent. Hæmorrhagic.
d. Variations in evolution . . .	Acceleration. Retardation. Abortion. Recrudescence. Persistence.
e. Variations in involution . . .	Inflammation. Suppuration. Ulceration. Gangrene.
f. Variations in healing and formation of scar.	Delayed healing. Induration. Cheloid.

a. Variations in Number.—This subject, which is necessarily of some length, will be more conveniently considered under the heading of Generalised Vaccinia (*q.v.* p. 679).

b. Variations in Size.—Two, three, or four of the compound vesicles resulting from ordinary vaccination, may coalesce to form one large pock, the size of which may be almost indefinitely increased by the development of supernumerary pocks in the immediate neighbourhood of the primary vesicles; an example has been recorded by myself (1) (*vide* Fig. 15, p. 679) in which the sore on the arm thus produced measured 4 inches by $4\frac{1}{2}$ inches. These cases as a rule are not serious; with cleanliness and protection of the arm from injury, the sores heal well and quickly.

c. Variations in Contents.—Under certain conditions, the most important of which are a cachectic state of the vaccinated child, the use of contaminated lymph, or the improper treatment of the vesicles (*vide* Vaccinal Ulceration, p. 725), the contents of the pocks, instead of being clear and bright at the end of the first week, may be watery and unhealthy, or pus may have formed early, or the contents of the vesicles may be hæmorrhagic: any one of these conditions may be of grave importance.

d. Variations in Evolution.—(i.) The development of the pocks may be accelerated by the season of the year—it is more rapid in warm weather than in cold—it is influenced by the idiosyncrasy of the individual, and also by the amount and activity of the lymph used. Their development is also accelerated by the degree of immunity which has been attained by previous vaccinations. Thus Cory (9C) found by vaccinating in series, one insertion being made on each of eleven successive days, that

all the successful insertions came to maturity on the ninth day. The insertions made subsequent to this date were ineffectual. He also found (9D) that in cases in which vaccination was performed on supernumerary fingers which were removed on the fifth day, vaccination performed in the usual way a month later hurried through its cycle, as happens in the revaccination of individuals in whom immunity has not been completely secured.

(ii.) Retardation of the pocks may be brought about by the converse of such conditions, the evolution of vesicles being delayed for ten, fifteen, or possibly even thirty days (37); and in some cases vesicles which seemed to have aborted entirely were excited to activity by a revaccination a week or more after the first insertions.

(iii.) The recrudescence of a pock and its breaking down after an interval of some weeks has been noted in cases of invaccinated syphilis (p. 718), and should at any rate excite suspicion as to the purity of the lymph. No allusion is here made to those cases of ulceration of pocks which not infrequently result from some mechanical injury to the scabs.

(iv.) The non-development or abortion of pocks at the points of vaccination probably depends largely on the quality of the lymph and the experience of the vaccinator. The "insertion-success" of skilled vaccinators is very large, amounting to 97-98 per cent.

Morrow (42A), under the heading of false or spurious vaccinia, gives the following varieties of the evolution of the pock by the production of (*a*) a vesicle containing opaque or straw-coloured lymph, complete on the 4th-6th day, and with an irregular involution; (*b*) a small reddish tubercle, which matures by the 4th or 5th day and disappears, leaving no cicatrix; (*c*) a single bulla, or a group of herpetic vesicles, which soon burst and cause irritation by the exuded fluid; (*d*) a vesicle running a normal course until the 8th or 9th day, when it ruptures, and a scab forms with ulceration beneath it; (*e*) a pigmented tubercle, "supposed to be the product of bovine lymph," the so-called *raspberry sore*. It is formed during the second week after vaccination by the coalescence of a number of small papules reaching the size of a large pea or coffee grain. It is preceded and followed by intense itching, lasts 4 to 8 weeks, and disappears, leaving pigmentation but no cicatrix.

e. Variations in Involution.—As has been observed, a hard-and-fast line cannot always be drawn between the local manifestations which result from vaccination in a normal case, and those which so far exceed what is necessary or desirable, as to constitute a source of danger to the individual vaccinated. As regards the vesicles it will be found, that besides those departures from the normal which have been indicated above, many of which may be considered as of little consequence, complications such as severe inflammation round the pocks, ulceration, coalescence of several pocks into one large ulcer, and even local necrosis of the tissues in the region of the pocks, may occasionally occur. Abnormal results in vaccination depend on so many factors—the lymph,

the method of vaccination, the treatment of the vesicles, the condition of the individual vaccinated, both previous and subsequent to the operation—that it may be by no means easy in a given case to trace their origin, to detect the cause, or to predict their occurrence; such results may, however, be expected to follow the careless treatment and injury of the vesicles, the vaccination of feeble or sickly children, lack of care, and unsuitable feeding of children during the vaccination period, or the use of lymph which has been improperly stored, or collected from vesicles with obvious inflammation about them. A further cause of danger possibly lies in the vaccination of children who have recently been exposed to, or who are incubating, some acute disease, such as scarlet fever or measles. These dangers may be almost entirely avoided if the precautions enjoined in the instructions to Public Vaccinators (Vaccination Acts 1867-1898, Third Schedule, Para. I.) are faithfully carried out, but they do occasionally arise, and the examples given will serve to shew that a large number of the inflammatory complications which follow vaccination are directly traceable to some extraneous cause, and cannot in any way be considered merely as variations in the involution of the normal vaccine pock. The cases of suppuration, ulceration, and gangrene are, however, of so much importance that they will be considered under the heading of Vaccinal Injuries (p. 696).

f. Variations in Healing and Formation of Scar.—Vaccination wounds, under normal conditions, should be well and firmly healed before the end of the third week; but in rare cases they may remain open for many weeks, or in still rarer instances, for months. This delay in healing is often due to easily preventable causes, such as repeated injury to the scabs—by other children, by shields, dirty sleeves, dirty applications—and general want of cleanliness; sometimes it is due to the feeble condition of the child combined with unfavourable surroundings; and, though no doubt in exceptional cases the ulceration is definitely started by vaccination, in most of the instances which have come under my notice I have found that extraneous conditions are, as a rule, far more to blame for prolonged ulceration than any inherent defect in the lymph or in the method of vaccination. Such cases of deferred healing are not infrequently mistaken for vaccinal syphilis; and a protracted investigation into a series of such cases, made by Sir T. Barlow and myself, will be found in App. ix. to Final Report of R.C.V. 1896, pp. 320-329. The means by which a diagnosis may, in most cases, be made with certainty will be found under the head of Vaccinal Syphilis (p. 727).

Although, as already indicated, the scar left by vaccination conforms, as a rule, to a general type, its appearance may present very considerable variations. There is nothing peculiar to vaccination in these abnormalities; they depend largely on the amount of inflammatory reaction at the seat of inoculation. The changes which are most frequently met with are simple hypertrophy or puckering of the scar, and cheloid. None of these conditions indicate that the operation

has been unsuccessful; and no certain deduction as to the course of vaccination can be made from them. I have seen a case of cheloid, for instance, which followed on vaccination made by subcutaneous punctures in which no true vesicles resulted; and Mr. Hutchinson has recorded a case which followed after protracted ulceration of the pocks (28). There is some ground for supposing that the occurrence of cheloid depends on the idiosyncrasy of the person, since there is not only a tendency for the condition to spread beyond the limits of the original scar, but, if removed, it is prone to recur (23A).

Lupus of the vaccination scars is discussed on p. 733.

General symptoms.—These are commonly unimportant; sometimes a slight rise of temperature is noted about the 3rd day after inoculation: this may be followed by remissions, and if there be any fever it generally reaches its maximum before the 8th day. These slight disturbances are often the only evidence of a general diffusion of the virus, although eruptions such as erythema, roseola, or urticaria may accompany even the mildest and most favourable cases of vaccination. These rashes, which may develop early in children who are unusually susceptible[1] to the vaccine virus, may occur within four or five days of inoculation, or they may develop during the period of maturity and subsidence of the pocks; they have no special significance, and, as a rule, are not harmful except in so far as they produce irritation and consequent restlessness. Amongst the more usual complications which occur at or about the period of the full development of the pocks are those which are common in all the acute exanthems; such as headache (in adults and in elder children), lassitude, irritability, sleeplessness, disturbances of the digestive system — *e.g.* anorexia, vomiting, catarrhal diarrhœa; and possibly, during the onset of the vaccinal fever, rigors may occur in adults and in the revaccinated, and convulsions in infants. In relation to these indications of a general infection, there will in some instances be evidence of a corresponding disturbance of the circulatory or respiratory apparatus, as shewn by increased rapidity of pulse and respiration, bronchial catarrh, or slight temporary albuminuria.

Fürst (23) points out that there is an increase in the number of leucocytes in the blood during the vaccination period. This increase takes place about the 3rd day, when the local eruption is first developing; and again when the surrounding inflammation is at its height. The leucocytosis diminishes rapidly with the fall of temperature in the early part of the second week, and appears to be proportional to the severity of the symptoms.

[1] The problem is generally thus stated, and although children differ widely in their reaction to all kinds of external stimuli, increased susceptibility to the vaccine virus must in our present state of knowledge be held only to imply that the effect produced by vaccination in a particular case is unusually severe. For various reasons one child may receive a much stronger dose than another, and the apparent greater susceptibility of one child over another may possibly mean only that he has received a larger dose of the virus.

PART II

VACCINAL ERUPTIONS AND COMPLICATIONS [1]

Introduction.—Before taking up the general question of vaccinal injuries, attention may be directed to some of the more usual complications which are met with after vaccination: of these the most obvious are the cutaneous eruptions which, although they frequently accompany and sometimes result directly from the inoculation of vaccine lymph, yet for the most part are not peculiar to vaccination, but are common both in infants and adults, and arise from the most diverse causes.

That eruptions of various kinds follow vaccination is now generally recognised. They are as a rule harmless and of simple well-known forms, such as occur in all persons, especially in the very young, under the influence of irritants of widely different kinds and acting in various ways. The rashes produced by belladonna, potassium iodide, mussels, hydatids, septic infections, and antitoxins are familiar to all of us; many of the vaccinal eruptions, however much they may differ in the strictly pathological sense, are clinically of the same kind, and are probably due to a similar cause. Some of them have obtained a fictitious importance in view of the suggestion that an analogy exists between syphilis and vaccinia, on the ground that amongst other symptoms roseolous and other eruptions are common to both. The suggestion is of little value when it is remembered that similar eruptions are common after infection by diseases differing as widely as variola and cholera.

From such data as are available it seems probable that these rashes, which are by no means peculiar to, or characteristic of, vaccinia, signify only that a generalisation of the virus has taken place as the result of the local inoculation; and, further, it seems reasonable to conjecture that they are excited by some chemical irritant, as distinguished from those which, like erysipelas, are due to micro-organisms.

Vaccinal eruptions are usually characterised by their temporary duration and irregular distribution, and by their occurrence during the period of vaccination; they are often attended with much irritation, considerable general disturbance, and some pyrexia.

All kinds of eruptions occurring after vaccination are not infrequently attributed to it; as for instance those of scabies and acne, or even the rash produced by potassium bromide administered medicinally. A case of the latter kind [2] came under the care of Dr. Colcott Fox (22A). A mother who was suckling her child suffered from epilepsy, for which she was taking large doses of potassium bromide: the infant after vaccination

[1] A summary of this subject containing much useful information has been given by Mr. G. Pernet (158).

[2] A drawing of a similar eruption alleged to be vaccinal is given in the report of the Medical Officer of the Local Government Board, 1888, p. 28.

suffered from a plentiful crop of bromide pustules, which disappeared immediately the drug was omitted.

In making the diagnosis of a vaccinal eruption it is necessary to bear in mind these possibilities of error, since these symptoms may easily excite unnecessary alarm or suspicion in the minds of those who are responsible for the care of recently vaccinated children.

Classification and Chronology. — Various classifications of these eruptions have been made, of which the most satisfactory are those given by Mr. Malcolm Morris and Dr. Crocker (11, 12), to whose works I am much indebted.

CLASSIFICATION OF ERUPTIONS AND OTHER COMPLICATIONS FOLLOWING VACCINATION

Eruptions peculiar to vaccination.

1. Those which may result from the inoculation of uncontaminated vaccine lymph :—
   (*a*) Multiplication of vaccine vesicles by diffusion through digestive, circulatory, or other systems — generalised vaccinia.
   (*b*) Multiplication of vaccine vesicles by auto-inoculation.
2. Those probably due to some contamination of the lymph or to some peculiarity on the part of the individual vaccinated—vaccinia gangrenosa ; vaccinia hæmorrhagica.

Eruptions not peculiar to vaccination, which may be excited by the absorption of many kinds of virus ; probably due to chemical irritation, not to microbic infection.

1. Urticaria ; Lichen urticatus.
2. Erythema multiforme.
3. Roseolous, papular, vesicular, pustular, bullous eruptions (11, 37).
4. Eruptions resembling those of measles and scarlet fever.

Complications not peculiar to vaccination, which may result from the infection of any wound, and are due to some peculiarity on the part of the individual vaccinated, or to the introduction of some extraneous virus into the wounds at the time of vaccination or subsequently.

1. Probably due to peculiarities of the individual : Eczema ; Psoriasis ; Pemphigus ; Local Gangrene.
2. Probably due to some microbic infection of the wounds : Impetigo contagiosa ; Tinea tonsurans ; Furunculosis ; Glandular abscess ; Cellulitis ; Erysipelas ; Septic infections ; Tetanus.
3. Causation doubtful ; possibly due to microbic infection : Purpura.

Inoculated diseases.

Syphilis ; Lupus ? Tuberculosis ? Leprosy ? Cancer ? Epizootic disease ?

The dates at which these eruptions or complications may be looked for after vaccination are as follows :—

1. During the first three days : Erythema ; Urticaria ; Vesicular and bullous eruptions ; Invaccinated erysipelas.
2. After the third day and until the pock reaches maturity : Urticaria ; Lichen ; Lichen urticatus ; Erythema multiforme ; Accidental erysipelas.
3. About the end of the first week, and generally after the maturation of the pocks : Generalised vaccinia—(*a*) by auto-inoculation, (*b*) by general infection ; Impetigo ; Accidental erysipelas ; Vaccinal ulceration ; Glandular abscess ; Septic infections ; Gangrene.
4. After the involution of the pocks : invaccinated disease, for example syphilis.[1]

The dates at which the various eruptions or complications of vaccination appear after the operation are of considerable importance, as shewing the true nature of those cases in which the suspicion of invaccinated syphilis has been raised ; and the more so as some writers have endeavoured to trace analogies between vaccinia and syphilis. Thus, Dr. Creighton (10) states that "the real affinity of cow-pox is not to small-pox, but to the great pox. . . . The vaccinal roseola is not only very like the syphilitic roseola, but it means the same sort of thing."

It may be pointed out that the vaccinal roseola appears within a week of inoculation, syphilitic roseola not, as a rule, for a month ; that roseolous and erythematous rashes commonly usher small-pox, and occur very frequently after the injection of antitoxins — diphtheritic and others ; and again that the date of their appearance and the absence of any distinctive characteristic are opposed to the deduction that they are in any way allied to syphilis.

There does not seem to be adequate ground for concluding that, with the exception of generalised vaccinia, any of the eruptions enumerated above are peculiar to vaccination, or are an essential part of it. Their occurrence in a small number of cases is undoubted ; in some instances they certainly depend on extraneous and, therefore, removable causes, and in others they depend on peculiarities in the individual which are often unsuspected at the time of operation, and cannot be foreseen.

Nothing would be gained by discussing in detail all the various forms of eruption which may follow vaccination. None of them has any peculiar significance ; many of them are unimportant, and are only mentioned because they are sometimes a cause of anxiety to those who are unacquainted with their harmless character. The more important

[1] The general use of calf-lymph has rendered this accident impossible, except by some gross and inexcusable neglect of ordinary precautions.

eruptions, and some of the more troublesome,—such as eczema and impetigo,—require further notice; erysipelas, syphilis, tubercle, and

FIG. 11.—Supernumerary vesicles. Stage i. Discrete. Drawing made on 9th day after vaccination with lymph, 46th remove from the calf, and 4th remove from H. T. (*vide* Fig. 15, p. 679). For details, see Case 214, Appendix ix. to Final Report R.C.V., p. 402, No. 500.

leprosy, will be considered later in detail, although the three latter are mainly now of historical interest only.

From a clinical point of view the eruptions peculiar to vaccination are, without doubt, the most interesting and important; for if there be any connexion between vaccinia and variola, it might be expected that cases would occur from time to time in which the symptoms following vaccination would more closely resemble inoculated variola than the merely

FIG. 12.—Supernumerary vesicles. Stage ii. Semi-confluent. Drawing made on 14th day after vaccination with humanised lymph.

local phenomena which are generally associated with vaccination. Such cases do in fact occur; and, though the instances are rare in which vaccination is followed by a general eruption of pocks like those at the point of inoculation, it is (judging from my own experience) by no means very

uncommon to find the original insertions surrounded by supernumerary pustules, cf. Figs. 11, 12, 13, so that the appearances closely resemble the drawings of inoculated small-pox by Kirtland, reproduced in the *British Medical Journal*, 1896, vol. i. p. 1276. I do not intend to maintain that this resemblance implies of necessity any community of nature between variola and vaccinia, possible as this may be for reasons which are discussed by Dr. Copeman (p. 749), but it is found that, under certain conditions, the course of vaccinia departs from that which is ordinarily observed, and the affection becomes comparable to one of the exanthems, instead of being characterised only by a local pock without any general eruption. It is also worthy of note that conversely

Fig. 13.—Supernumerary vesicles. Stage iii. Confluent. Drawing made on 16th day after vaccination in four places with humanised lymph. First appearance of eruption on 9th day; eruption first confluent on 11th day. Besides the eruption on arm there was only one umbilicated vesicle on abdomen. Compare with Fig. 14, shewing inoculated small-pox, and Fig. 15, vaccinia confluent at point of inoculation in a later stage.

small-pox, by successive re-inoculations of the same individual, may shew itself only as a local pock at the point of inoculation without any general eruption (43, 49). This is the case not only in the direct inoculation of variolous lymph, but is equally so in "vaccinations" performed with lymph taken from pocks raised on the calf by the inoculation of small-pox virus. These points of resemblance between variola and vaccinia are of interest whether they indicate any close relationship between the two affections or not; there is little warrant, indeed, for the belief that generalised vaccinia is identical with variola: and (unlike small-pox), so far as I am aware, no case has been recorded in which vaccinia has proved to be communicable, except by direct inoculation, or by the ingestion of material from the vaccine pocks, although cases with a general eruption somewhat similar to variola do at times occur. I am not, however, aware of any

such case which has been proved to be contagious. See Pierce (45D).[1]

Generalised vaccinia differs in many ways from a general diffusion of vaccine pocks by auto-inoculation through the skin; though both affections indiscriminately have been called by the same name. For convenience of description Longet's classification of these generalised vaccinal eruptions may be adopted. It is as follows:—

1. Spontaneous general vaccinal eruptions or generalised vaccinia—Vaccinal eruptive fever.

2. Vaccinal eruptions generalised by auto-inoculation, for example,

FIG. 14.—Inoculated small-pox. Shewing the appearances of a single insertion on the 14th day. From the original drawing by G. Kirtland (1802), lent by Mr. G. W. Collins of Wanstead.

by scratching—(without any pre-existing lesion of the skin. T. D. A.) Multiplication of pocks by auto-inoculation.

3. To these should be added local vaccinal eruptions (often confluent), the occurrence and position of which are determined by some pre-existing cutaneous lesion such as impetigo, eczema, acne, or psoriasis. Some inevitable confusion has been caused by not clearly discriminating between vaccinal eruptions which have occurred on surfaces previously sound, and those in which the seat of the eruption has been determined by some previous local affection.

4. Vaccinal eruptions by migration.

These are too rare to be of any practical importance since they consist of those cases of generalised vaccinia in which the general eruption is the

[1] For an apparent exception to this see Martin's case, p. 682, which does not, however, really invalidate the truth of the general rule as stated above.

primary manifestation, no local result having followed at the point of inoculation. (Longet, *loc. cit.* p. 205.)

Generalised vaccinia, or vaccinal eruptive fever, occurs, as a rule, comparatively early after vaccination; either one or two days before or one or two days after the pock at the seat of inoculation has arrived at

FIG. 15.—Vaccinia confluent at point of inoculation, shewing the ulcerated surface left after removal of the scabs. There are two supernumerary pocks on the forearm. The drawing was made 43 days after vaccination. For details of case see p. 687; also Case 214, Appendix ix. to Final Report R.C.V., p. 402. Figs. 16 and 17 are from the same case.

maturity, that is to say, generally not before the 4th day or after the 10th. The date of its appearance may, however, vary considerably. In Poole's case (App. ix. R.C.V. No. cxciv. p. 70) the eruption began on the 13th or the 14th day (46); in Dr. Colcott Fox's two cases on the 9th day (22). The pocks form in successive crops, so that at a given date they may be found in all stages of development; in the three cases alluded to, the eruption continued to appear from the 13th to the 28th day, from the 9th to the 19th, and 9th to the 16th days respectively. When it first appears the

eruption is dusky red, then rapidly becomes papular, vesicular, and finally pustular; in two or three days the pocks arrive at maturity, and sometimes closely resemble the original vaccine vesicles: in other cases they so much resemble those of variola that Bousquet declares that there is "so much resemblance between vaccinia and inoculated variola that no physician, however experienced, is in a position to differentiate the vaccinal from the variolous pustule. The most sagacious make mistakes. In a word, at whatever period you select—the 7th, the 10th, the 12th, or 15th day—the characters of the one are the characters of the other. There is no difference between them." [1] (Fig. 14.) This is hardly the case, since the eruption of inoculated variola appears about the 12th (9th-14th) day. Generalised vaccinia, as a rule, appears earlier (about the 7th day); and the vaccinal fever is generally less pronounced and the constitutional disturbance less marked than in the case of variola. It is not usual for the vaccinal eruption to be found on the mucous membranes or conjunctivæ; but this distinction does not hold good in all cases. Two instances in which the mucous membrane of the mouth was affected, and one in which the vesicles formed on the conjunctivæ, have been noted in England. (See L.G.B. Reports, Nos. li. and clxii. App. ix. to Final Report of R.C.V. 1896, pp. 20 and 56.) The similarity of the two affections is such that the suspicion of variola was raised in not a few of the recorded cases before the nature of the eruption was recognised (27, 29, 40A, 41, 46).

The table on the opposite page, founded on that given by Dauchez, gives the chief points of difference between variola, inoculated variola, and generalised vaccinia—eruptive vaccinal fever.

[1] An interesting case is reported by Dr. Sharkey (52), "A case in proof of the non-identity of variola and varicella." In this instance, a boy who may have been exposed to the contagion of small-pox (though this is not certain) was admitted to St. Thomas's Hospital suffering from chicken-pox. He was vaccinated, and eight days afterwards an eruption believed to be small-pox began to make its appearance. If generalised vaccinia can be determined by a cutaneous eruption, it is conceivable that this was in fact a case of that disease; and in this connexion attention may be called to a remark by Dr. W. J. Simpson, whose researches into the relation of variola and vaccinia are well known (53):—"Vaccine and chicken-pox have always seemed to me to be two elements of small-pox which have become separated in some unknown way; the vaccine retaining the peculiar qualities which affect the body in such a manner as to render it immune from a second attack, while chicken-pox has none of these qualities."

[Table

Day.	Variola (33).	Inoculated Variola (57, 34).	Vaccinal Eruptive Fever (Generalised Vaccinia).
1.	Contagion.	Inoculation.	Vaccination.
3.	Period of incubation.	Papule at point of insertion becoming vesicular: vesicle prominent, slightly umbilicated.	Papule at point of insertion becoming vesicular. Supernumerary vesicles form between 3rd and 9th days.
7.	,,	The local pock fully developed by the 7th day.[1]	7th-8th day slight pyrexia.
9. 10. 11.	Malaise, rigors, pain in back, vomiting, reddening and enlargement of glands.	Inflammatory areolæ, 10-15 pustules form round points of inoculation; headache, vomiting, pain in back, slight fever.	Maximum of development of pustules, which gradually decrease until the 16th or 17th day.
12.	..	Between the 11th and 13th days the specific eruption of variola appears, generally discrete and resembles varioloid.	
13.	Erythematous or roseolous eruptions followed by specific papular eruption on face, wrists, flexor surfaces of arms, etc.	...	The extent of febrile reaction seems to depend on the extent and nature (discrete or confluent) of the eruption, as well as on unessential complications such as ulceration of pocks, excessive local reaction.
15.	Remission of fever.	..	Besnier considers that there is no pyrexia unless there be some complication, for example, glandular enlargement.
17.	Papules become vesicular and umbilicated.	...	Subsidence of eruption generally complete before 21st day.
20 to 22.	Eruption becoming pustular. Secondary fever.		
	The exanthem is contagious.	The exanthem is contagious.	The exanthem is only communicable by direct inoculation of one individual from another.

[1] The local eruption of inoculated variola is not complete until the 7th day, according to Rayer (47); the general eruption developing from this date, but not being complete until the 13th or 14th day.

The only decisive test whether an eruption following vaccination be a true "vaccinide" or not is that lymph taken from one of the vesicles

at a distance from the original point of inoculation shall be capable of reproducing the specific effects of vaccination in an animal, or in another child (19). That this can be done has been shewn by Richard and by Martin. In the former case 15 children were successfully vaccinated; and in Martin's case a heifer was successfully vaccinated from pocks which developed in a child suffering from a general eruption, resulting, as it would appear, from its being suckled by its mother during the period of her vaccination. An interesting demonstration of the true nature of the supernumerary pocks was given in a case of vaccinia generalised by auto-inoculation, reported by myself (1), in which the child suffering from pocks on its lips and face inoculated its mother's breast; the subsequent vesicle shewed no departure from the ordinary appearances or evolution of a vaccine pock.

Causation of Generalised Vaccinia.—Apart from any peculiarity of the lymph, and without assuming abnormal receptivity on the part of the individual, the eruption of vaccination may cease to be purely local if the virus be administered, not through the skin, but by the digestive, circulatory, or respiratory systems; and also (apart from auto-inoculation, which is considered later) if during the vaccination period there be some co-existent, general cutaneous eruption, such as sudamina.

A generalised vaccinal eruption has been produced in children who had sucked their vaccination pocks;[1] and it has been determined in those who had previously proved insusceptible to vaccination, by the intentional administration of powdered vaccine crusts with food (7). Similarly, as has been noted, a general vaccinal exanthem has appeared in a child suckled by its mother who was undergoing vaccination (41).

It is of interest in connexion with this latter case to note that certain children, whose mothers have been successfully revaccinated previous to their confinements, have been vaccinated shortly after birth without result; shewing, possibly, that the effect of the mother's vaccination was shared by the fœtus in utero. In investigating this point a large number of observations have been made; the most remarkable of which are those of Burckhardt and Kellock on women, and those of Rickert on sheep. Burckhardt vaccinated 28 pregnant women, and subsequently vaccinated 6 of the children whose mothers had been successfully vaccinated. The operation was unsuccessful in all of them. Kellock vaccinated 36 women in various stages of pregnancy, and found (*a*) that the infants resisted vaccination directly as the stage of pregnancy at which the mother was vaccinated; and (*b*) that the fœtus seemed to be more readily affected in the multiparous than in those of a first pregnancy. His results were as follows:—Of 14 children of primiparas, vaccination was successfully performed on the infant in every case in which the mother had been vaccinated earlier than the seventh month of pregnancy; whilst the operation failed in 5 of the infants whose mothers had been vaccinated later than the seventh month. In the case of the children of the multiparas, no less than 16 proved insusceptible to vaccination, even though in some

[1] Étienne: quoted by Longet.

of the cases the mother had been vaccinated as early as the fifth month. These facts are corroborated by an observation made by Depaul (18), that variola may be transmitted from the mother to the fœtus in utero, and also by some observations recorded in the *Transactions of the Epidemiological Society* (1885-86, vol. v. N.S. p. 166), from which it appears that vaccination failed in three infants whose mothers had suffered from small-pox more than 16 days previous to their confinements, but was successfully performed on three children whose mothers sickened with the disease less than 8 days before the onset of labour. Some further clinical evidence on these points was brought forward during a discussion in the *British Medical Journal* "on the effect of revaccination during pregnancy on the child." Dr. Ballantyne (2*a*) is of opinion that one fœtus in three is protected by the vaccination of the mother during the second half of pregnancy; but it seems probable that the immunity so produced is transient and not comparable with that which results from vaccination by the usual method.

Some experiments of Straus, Chambon, and Menard have a bearing on these points. They found that the blood-serum of a calf, taken before the pocks were healed, produced temporary immunity in other animals of the same species when introduced into the venous system. Chauveau has also demonstrated that a generalisation, manifested by an eruption capable of reproducing the ordinary results of vaccination, could be excited by the infection of horses through the digestive, circulatory, and respiratory systems, as well as by injection into the subcutaneous tissues.

These observations, which are in agreement with the clinical facts, prove that the results of vaccination may be obtained without the production of the local pock: and under given conditions the diffusion of the virus is occasionally demonstrated by the appearance of a cutaneous eruption similar to that which occurs in the acute exanthems, even if it be not entirely analogous to them.

Vaccinia generalised by auto-inoculation.—Allied to spontaneous generalised vaccinia are those sequels of vaccination which are caused by the more or less wide distribution of vaccinal pocks by auto-inoculation. These supernumerary pocks may be caused by scratching with the nails after they have been in contact with the vaccine pocks; or by accidental contamination of surfaces denuded of epithelium by any such cause as eczema, impetigo, psoriasis, or other cutaneous eruptions which cause a breach of surface; they may be produced in any part of the body accidentally brought into contact with virus from the vaccine vesicles. Such cases are common, and references may be found to them in the papers already referred to, especially Dauchez, Longet, and Poole (14, 36, 46): drawings of remarkable cases are given in my paper in the Clinical Society's *Transactions*, 1893, vol. xxvi. p. 114, pl. ii., and in Dietter's paper. The number of pocks varies from one or two upwards; and in the cases in which the eruption has become confluent the number is often very great. Most of these cases are unimportant, and result

only in a little temporary inconvenience, even if the eruption occur on the cheek, lips, tongue, ears, buttocks, or breast (1, 29, 35, 40, 51); accidents, all of which (21B) have been placed on record.[1] Such accidental inoculations have been brought about by the use of hand-

FIG. 16.—Vaccinia generalised by auto-inoculation. From a drawing made by Miss M. Green on the 43rd day after vaccination. The pocks *a*, *b*, *c*, *d*, *e*, were about 14 days old; *f*, about 56 hours. *Lymph*, humanised; 42nd remove from calf. *Eruption* round points of inoculation confluent on 14th day. See Fig. 15. *Pocks* continued to appear until the sixth week after vaccination. Mother's breast was inoculated, and the pock ran a normal course. For reference to details of case, see p. 687.

kerchiefs, sponges, ointments, baths, and beds which have been used for recently vaccinated infants; and they may occur in the most unexpected ways, as, for instance, in the case of a man who, having chafed himself

[1] See also for references, Sub. "Vaccine Ophthalmie," Fürst's *Die Pathologie der Schutzpocken-Impfung*, p. 104.

in riding, applied some vaseline to the sore place out of the same pot which his wife had used for the arm of their child who had been recently vaccinated: the result was a large crop of vaccine vesicles on the buttocks. If vesicles occur on the eyelids (2D) or the eyeball, the consequence may be serious; this latter accident, however, is of great rarity. In five cases recorded by Mr. Berry the ulceration was confined to the eyelid. The symptoms vary with the seat of the initial lesion and the condition of the patient as regards immunity against vaccinal inoculation (1, 21, 26, 56).

FIG. 17.—Vaccinia generalised by auto-inoculation. Pocks from various parts of the body. *c* measured about $\frac{1}{2}$ in. transversely; *e*, $\frac{3}{8}$ in.; and *f*, $\frac{3}{8}$ in. The drawings were made on the 43rd day after vaccination: *c* was then about 12 days old, and *e* and *f* about 14; *d*, about 48 hours. There was little inflammatory thickening round them; no true induration. In the centre of *e* and *f* there was a clean granulating surface. Cf. Figs. 15, 16.

Thus infection of a mother's eye by her child's finger may result in a well-developed vaccine vesicle, infection of the child's own eye after the 8th day may result in an abortive pustule, or in an ophthalmia such as may be produced by any chance contamination with pus, as, for instance, in gonorrhœa. Although the name of vaccine ophthalmia has been given to the affection (Saemisch), there does not seem to be any adequate ground for supposing that it stands in any essential relation to vaccinia, or is other than a purely accidental complication. An inquiry by Hulke into the alleged occurrence of blindness amongst the pupils at the Royal Normal College for the Blind, Upper Norwood—in which institution, if

in any, such cases would probably be found—resulted in the conclusion that, of eight cases alleged to be caused by vaccination, seven were conclusively proved to be due to some other cause; and in the one doubtful case Hulke found no grounds for attributing the event to the cause alleged.[1]

One other form of accidental auto-inoculation calls for special notice, since mistakes in diagnosis might occasion much unnecessary distress. Cases have been recorded (16, 54, 55) in which sores were produced around the anus, and on the mucous membrane of the vulva, by the accidental transference with the fingers of pus from the vaccinated arm. It is hardly necessary to point out that such sores, especially if macerated by the contact of the parts and ulcerated, might be looked upon as venereal (as has actually been done) if due care were not exercised. A knowledge of the possibility of such an occurrence and the history of the case ought to prevent this error, even if (owing to the position of the sore, and the stage of evolution of the original vaccine vesicle from which the infective material was derived) the characteristic appearances of the vaccine pock should have been lost.

A definite case of local confluent vaccinia, in which the eruption became generalised by auto-inoculation and possibly also by absorption of the virus through the digestive tract, has been recorded by myself. In this case it would seem that the abnormal conditions were primarily due to some peculiarity on the part of the child, since the lymph used was the forty-second remove from the calf; and three other children were successfully vaccinated from the child without complication of any kind. The lymph was traced backwards and forwards for three generations: and twenty-five children in all were examined in immediate relation to this particular case. The only abnormality detected was that in four out of eight children vaccinated with lymph from the same source, no result followed; whilst in one child, in the fourth remove, twelve supernumerary pocks appeared. A brief chronological summary of the case is given for reference :—

[1] In comparison with the above it may be interesting to record Dr. Brailey's observations on 763 persons, who for some cause or other had lost an eye: 15 of these had lost their sight from small-pox, of whom 7 (43 per cent) were unvaccinated and suffered from small-pox at an average age of 8·9 years, 4 with no vaccination scar at an average age of 8·2 years, 2 with one scar at an average age of 20 years, 2 with two scars at an average age of 28·5 years.

[TABLE

H. J. K., æt. three months; Vaccinated with humanised lymph, 42nd remove from calf. Generalised vaccinia; Death. (Figs. 15, 16, 17.)

First week . .	9th November 1892	Vaccination with humanised lymph, forty-second remove from calf. (Of eight vaccinations by three vaccinators with lymph from same source, four were unsuccessful, but without complication or abnormal result.)
Second week . .	16th November 1892	Inspection. Four healthy vesicles to all appearances normal.
Third week . .	23rd November 1892	The four pocks coalesced into one, and became covered with dark brownish green scab. Innumerable secondary pocks, at first vesicular, formed round points of inoculation, cf. Fig. 13.
Fourth week . .	30th November 1892	Secondary eruption pustular; a large pock appeared on back of head, which eventually scabbed and dried up. (Pocks appeared on face; arms, legs, abdomen, and thighs.)
Fifth week . .	7th December 1892	The supernumerary pocks at points of insertion confluent; eventually a large open sore formed.
Sixth week . .	14th December 1892	No improvement in child's condition.
	17th December 1892	Pulv. hyd. c. creta, gr. ½ given three times a day with some improvement. Pock formed above inner angle of left orbit.
Seventh week .	21st December 1892	Vesicle forming behind right ear; this aborted within 24 hours.
	25th December 1892	Child's condition worse. Mother's breast became inoculated from suckling the child. Pock ran a normal course. Mother had not been revaccinated.
Eighth week . .	27th December 1892	Death.

There is no evidence to shew that such cases are due to any particular strain of lymph, whether humanised or taken direct from the calf (51, 31); they are of great rarity, and must be regarded as accidental complications rather than as essential elements of vaccination.

Such a case as that narrated above opens out the whole question of vaccinal immunity, which it would be impossible to discuss at any length in this place. If the observations of Cory, Trousseau, Mognier, Dumont-Pallier, Damaschino, Besnier, and others are conclusive and final, there is evidence to shew that in ordinary circumstances the receptivity of an individual to successive vaccinations in series gradually diminishes during the second week, and usually becomes extinct before the fourth.

Cory (9c) found that when vaccinations were performed in series by a single insertion on each of eleven successive days, those made after the ninth day were unsuccessful, and he concluded that immunity was attained at this period. It is certain that during the first week after vaccination an individual may be readily revaccinated or may

contract small-pox; for it does not appear that any considerable degree of immunity is established until after the pocks have reached maturity. Immunity probably reaches its maximum about the fourth week after vaccination; but the standard of resistance varies with each individual, and probably also with the dose and activity of the virus. In the case given above, pocks continued to form for thirty days certainly, and probably longer; so that no rule can be made universally applicable. Vaccinia generalised by auto-inoculation may, however, be expected to occur, if at all, before the third week after vaccination.

Great variations may be met with in susceptibility to vaccinia as well as to small-pox or any of the acute exanthems. It is commonly recognised that one attack of small-pox renders the individual more or less immune against contracting the disease again; and similarly that one successful vaccination protects, at any rate for a time, against the probability of a second successful inoculation. But it would seem that in some persons one attack is no safeguard against a second. This is well illustrated by a case which came under the notice of Prof. Clifford Allbutt, in which a woman had small-pox three times, and was also three times successfully vaccinated. Such a case seems to set at defiance all laws deduced from ordinary observation, and may be regarded as the exception which proves the rule. The following table gives a brief outline of the facts:—

1858.—A. B.; born ——. Mother developed small-pox when infant was eight days old, and child had it in a mild form.
,, When three months old successfully vaccinated (three scars).
1881.—Successfully revaccinated (two scars).
1883.—Mild attack of small-pox.
1892.—(September). Successfully revaccinated (two scars).
,, (November). Unsuccessfully vaccinated.
1893.—Unsuccessfully vaccinated.
1896.—Very mild attack of small-pox; (but indubitable, T. C. A.)

There is strong evidence that this persistent falling away from immunity in this respect existed in other members of this patient's family.

Vaccinia hæmorrhagica.—Besides the cases in which the sequence of events and the appearance of the eruption are analogous to those found in the acute exanthems, there are others in which the pathological position is at present doubtful: in these cases vaccination is followed by an eruption which is more or less "hæmorrhagic." The eruption may vary in intensity, from the faintest petechiæ to general hæmorrhage; and may be characterised by a few scattered petechiæ, subcutaneous ecchymoses, or severe hæmorrhage from mucous membranes, such as hæmaturia. Such cases are extremely rare; and, although there is no direct proof of it, they are probably analogous to the well-known cases of hæmorrhagic small-pox and

scarlet fever.[1] They are too few in number to warrant any opinion as to their causation; but, apart from any peculiarity in the lymph, it might be expected that such complications would occasionally arise in scorbutic, rachitic, and cachectic children; the cause which determines the nature of the eruption being rather the condition of the child than any abnormality of the lymph.

Vaccinia gangrenosa.[2]—A disease closely allied to generalised vaccinia, if not a modification of it, has been described by Mr. Hutchinson (29), Stokes (54), Dr. Crocker (11), and others, under the name of vaccinia gangrenosa. It is to be regretted that this name has been used for another affection of quite a different character; namely, local gangrene or necrosis at the points of vaccination (46A). Vaccinia gangrenosa is an acute exanthem occurring at the end of the first or the early part of the second week after vaccination. The eruption begins in the form of discrete papules with an inflamed base, which ulcerate and scab over, pus forming under and round the scab, while the ulceration extends both in depth and laterally. In this way a central black slough is formed, which after its removal leaves an irregular, unhealthy ulcer, often with overhanging edges. The ulcers may be single or confluent. In Dr. Crocker's case, from which the above description is taken, the largest ulcers were $\frac{3}{4}$ in. in diameter and $\frac{1}{3}$ in. in depth.[3] Mr. Hutchinson considers that the diagnosis of these cases lies between variola, varicella, and vaccinia; and Dr. Crocker includes in his account of the disease a fourth affection, "dermatitis gangrenosa," independent of any one of those named, and probably due, as he believes, to some pathogenetic organism—possibly the *Bacillus pyocyaneus*. It is not yet possible to state the precise relationships of these cases, but it seems certain that the eruption can be determined by vaccination, and probable that the disease is a true exanthem, possibly allied to small-pox or chicken-pox; but there is no evidence to decide whether it be due to a mixed infection, or is the direct result of a specific virus acting upon an individual whose tissues are altered by syphilis, tuberculosis, rickets, or other constitutional malady, all of which have been considered as favouring its production.

Eczema.—Vaccination is performed, in the majority of cases, at a period of life when eczema and other inflammations of the skin are extremely common; and it is no wonder that the operation is sometimes followed by an acute outbreak of such disorders. I have not met with any case in which it seemed probable that the affection was transmitted by the operation; and in many cases which have come under my observation, and which have been recorded by others, the acute attack

[1] See 3 cases recorded by Dr. Gregory, Bergeron and Barthelemy, Dauchez, *l.c.* pp. 137-139.

[2] For illustrations see Mr. Hutchinson's paper (29) and Dr. Crocker's *Atlas of Diseases of the Skin*, pl. xli. fig. 1.

[3] Mr. Hutchinson refers (*loc. cit.* p. 5) to models 206 and 209 in the Guy's Hospital Museum, which he believes to be taken from cases of varicella gangrenosa. He also gives references to other cases besides his own. See also *Archives of Surgery*, vol. iii. 1892, plate xviii.

following vaccination or injury to the scab is merely a recrudescence of a pre-existing condition; or is an expression of a family tendency. Out of a total of 394 cases of alleged vaccinal injury which have more or less directly come under my notice during eight years, thirty, or about 7·5 per cent, were cases of non-specific skin eruptions;[1] and there does not seem to be any reason to suppose that vaccination is the specific cause of any large number of severe cases of eczema.

The statistics of 600 cases of eczema which had been under the care of Dr. Colcott Fox shew that 249 (41·5 per cent) came under treatment before the end of the first year; and in forty of these cases eczema is known to have occurred before vaccination. Of 161 cases in which the date of onset is recorded the eruption commenced in eighty before the end of the third month, and in sixty-nine during the next three months. This seems to give prima facie ground for supposing that vaccination is not responsible for any considerable increase in the number of cases; which is the conclusion drawn by Dr. Fox. At the same time it must be noted that there is a definite rise in the numbers in the fourth and in the ninth months, the periods at which the irritation of vaccination and of teething respectively, might be expected to come into play. The numbers are as follows:—

0-1 month	33	6- 7 months	10
1-2 months	22	7- 8 ,,	4
2-3 ,,	25	8- 9 ,,	23
3-4 ,,	39	9-10 ,,	1
4-5 ,,	23	10-11 ,,	1
5-6 ,,	7	11-12 ,,	3

In some instances an eczema which has been intensified by vaccination subsequently improves; but as a rule a pre-existing eczema is made distinctly worse by vaccination, and not only is it undesirable to vaccinate an eczematous child on account of the risk of aggravating the affection, but also because there is danger of causing a generalised vaccinal eruption on the affected parts.

Impetigo or Porrigo.[2]—The occurrence of this contagious affection of the skin after vaccination is little to be wondered at when the conditions under which the children of the poor have to live, are taken into consideration. In any circumstances pus is readily inoculated from one individual to another, so that local superficial sores are produced; and when such a source of contagion is introduced into a household where the inmates are dirty, ill-fed, and overcrowded, it is obvious that ample opportunity is afforded for the spread of a purulent affection both from and to a vaccinated child. I have seen cases of impetigo which

[1] See Case 25, App. ix. R.C.V. 1896, p. 241, and Case 98, p. 273, and Cases 95, 102, 127, etc.

[2] For plates, see *Atlas of Diseases of the Skin*, New Sydenham Society, fasciculus x. pl. xxviii., and *Atlas of the Diseases of the Skin*, by H. Radcliffe Crocker, fasciculus x. pl. xxxix. and xli. Cf. also Cases 24, 82, 129, 196, App. ix. R.C.V.

have originated from injury to the vesicles by dirty sleeves, dirty shields, dirty night-clothes, by exposure to infection from purulent discharges in other children, by scratching the vaccination wounds and inoculating distant parts of the body with the finger-nails. A case was reported to the Commission as one of vaccinal injury in which the child was wearing a hat the lining of which was soaked with pus from an impetigo which had occurred a year previously. This instance well exemplifies the lack of attention to ordinary cleanliness, which is often a main factor in bringing about skin eruptions attributed to vaccination.

It is unnecessary to discuss this question at length: it cannot be doubted that impetigo may follow any wound, vaccinal or other, in which pus is formed; and that the liability to the affection is enormously increased by want of cleanliness and bad hygienic surroundings. It is a more serious question whether these disorders are ever actually communicated by vaccination. Impetigo is no doubt due to the presence of pyogenetic cocci in the discharges, so that it is possible that some lack of care in the selection of the vaccinifer might lead to the inoculation of one child from another. I have only investigated one case in which there was any evidence that such communication might have occurred; and in this instance the vaccinifer did not begin to suffer from impetigo until some days after the lymph had been taken from his arm, so that there was no proof that the child was capable of communicating the disease at the time that he was used as a vaccinifer. It is also possible that both vaccinifer and sub-vaccinee may have suffered from the subsequent eruption in consequence of accidental contamination of the vaccination wounds by the lancet used for the operation.[1]

In foreign countries groups of cases of impetigo have followed vaccination in such a manner as to leave little or no doubt that the affection was communicated by the operation.[2] The lesson to be learned from these cases is obvious; namely, that there is risk in using any individual suffering from a communicable disease as a source of lymph.

Tinea tonsurans.—The accidental inoculation of the trichophyton tonsurans in the process of vaccination has been observed abroad (Hagar, Eichstadt), but I am not aware that any case has occurred in England. Like many other communicable skin diseases, it is common in poor and ill-cared-for children; and it is not surprising that in rare instances vaccination should be the means by which it is transmitted from one child to another.

Pemphigus; Psoriasis.—The occurrence of these affections after vaccination has been recorded (Dauchez (14), Rioblanc, Howe, and Tyzzer); and there is some evidence that in rare instances the virus which causes them is transmitted by the operation. A valuable contribution to the discussion of the subject will be found in a paper by

[1] See Case 180, App. ix. R.C.V. p. 366.

[2] See Fürst, *loc. cit.* p. 72, and Third Report R.C.V. 1890. p. 135, and Peiper, *loc. cit.* p. 64.

Dr. Bowen, in which he refers to a series of cases of infectious pemphigus following vaccination, and also to analogous cases (including those recorded by Pernet 45c)) in butchers and others handling animal products.

It would appear from these observations that in some exceptional cases a causal relation may exist between epizootic disease in cattle and bullous eruptions occurring in individuals who have been vaccinated with lymph derived from an infected animal. There is, however, ample evidence that in some of the recorded cases the individual vaccinated was predisposed to, and had suffered previously from, skin eruptions similar to those which appeared subsequently; and that in others the child vaccinated was in a cachectic condition as the result of some affection, which had lain dormant until roused into activity by the constitutional disturbance of vaccination.

The influence of the exanthems on the course of vaccination is not easy to determine. It is certain that such chronic or subacute affections as eczema, impetigo, and possibly psoriasis, are not uncommon causes of generalised vaccinia (*q.v.* p. 679); but though there is some evidence to shew that an acute specific fever—such as chicken-pox—can determine and precipitate a general cutaneous vaccinal eruption it is certain that a person suffering from scarlet fever or measles can be vaccinated without producing any deviation from the normal appearance of the rash.

The difficulty of arriving at any precise knowledge on these points is greatly increased because the nature, extent, and variety of post-vaccinal eruptions have hitherto received inadequate recognition; so that cases of generalised vaccinia have been regarded as small-pox, and cases of erythematous, vesicular, or papular eruptions, as scarlet fever, chicken-pox, or measles.

It is probably rare for vaccination to be complicated by any one of the acute specific fevers; and still more rare, should this happen, for any abnormality to occur. In isolated cases it is often a matter of great difficulty to decide whether an erythematous rash is scarlet fever, or whether a vesicular rash is chicken-pox. Cases have come under my notice, as well as under that of others, in which there were grounds for supposing that errors of diagnosis had been made; as, for instance, cases in which a simple vaccinal eruption had been regarded as evidence of invaccinated syphilis.

It would not be unreasonable to suppose that the course of a vaccination performed during the incubation-period of scarlet fever or measles might be disturbed, and that the tissues at the point of inoculation might undergo necrosis similar to that which occurs in noma or cancrum oris; but even if such cases do occur, they are so rare that we are compelled to regard them as accidental complications which are inevitable in all conditions of life, and of pathological interest rather than of clinical importance. Dr. Hopwood, for many years resident at the London Fever Hospital, informs me that he has himself vaccinated a considerable number of persons in all stages of scarlet fever, and has

seen many in similar circumstances vaccinated by others, without any evil result. He has also seen persons vaccinated shortly before an attack of scarlet fever, in whom no serious complications have resulted. In estimating the importance of facts observed by the resident medical officer of a well-equipped hospital, it must be borne in mind that vaccination wounds are much more likely to pursue a normal course in the cleanly conditions of a hospital, than in the crowded and often filthy surroundings in which many children are compelled to live; and that, given a case of vaccination, complicated by scarlet fever, in some miserably poor home, it will be well-nigh impossible to decide with certainty which of the many unfavourable conditions had been mainly instrumental in bringing about any abnormal result which may occur.

There is reason to believe, however, that under favourable conditions normal vaccinia can run parallel with scarlet fever, chicken-pox, and even with small-pox, if the latter be contracted before immunity is secured.

The influence of congenital syphilis on vaccination.—The statement has not infrequently been made that it is difficult or even impossible to obtain a normal vaccine vesicle in a child who is suffering from congenital syphilis (5). This certainly is not the case. If the child be not cachectic, vaccination may pursue a normal course, and the vesicles may be good, giving no indication whatever of the danger of collecting lymph from them for further vaccinations. This is of the utmost importance in the selection of a vaccinifer if humanised lymph is used. If calf-lymph be used, as it may now always be, this risk can be entirely avoided. The diagnosis of congenital syphilis must be made from an examination of the child, and a knowledge of its family history; and no reliance whatever should be placed on the appearance of the vaccinated arm. If the vaccinated child be cachectic there is a danger that vaccination may be followed by ulceration or sloughing at the point of inoculation; or that some one of those complications may arise which occur in feeble children, who have little or no power of resistance against local inflammation.

The influence of vaccination on latent disease.—Symptoms of scrofula,[1] tuberculosis,[2] congenital syphilis,[3] sometimes occur after vaccination; and the lesions, without adequate ground, are apt to be attributed directly to vaccination. It is in accordance with ordinary clinical observation that disease, hitherto quiescent, should be lighted into activity by some factor which is not specifically concerned in its causation. Thus a mechanical injury, an acute specific fever, prolonged anxiety, or insufficient food, may be followed by pulmonary or meningeal tubercle, or by some other local manifestation of tuberculosis.

Although the vaccination age has been postponed from three to six

[1] Cases No. 131, p. 307, and No. 187, p. 374, Appendix ix. R.C.V. 1896.

[2] Case 187, p. 374.

[3] Cases No. 227, p. 413; No. 309, p. 438; and cf. Cases 198, p. 386; 202, p. 389; and 326, p. 447, *loc. cit.*

months, primary vaccinations are not infrequently performed at or about the period when symptoms of congenital syphilis may be expected to declare themselves; and cases have come under my observation in which children known to have been previously suffering from congenital syphilis have been vaccinated with humanised lymph, and in whom the subsequent evidences of syphilis have been put down to vaccination.[1] In a particular instance it may not be easy to prove that a lesion which follows vaccination is not directly the result of the operation; but in most instances the history of the case, if fully inquired into, will give conclusive evidence as to the real origin of the malady.

On drug-eruptions, which may be mistaken for vaccinal rashes.—The possibility of a post-vaccinal rash being in reality due to the internal administration of some drug must not be forgotten. Belladonna, the bromides, and possibly the iodides and arsenic, are not infrequently given to children, even to infants, and when it is remembered how susceptible some individuals are to such drugs and what a variety of eruptions are produced by them, it is little to be wondered at that, in rare instances, a drug eruption is mistaken for a vaccinal rash. Bromide of potassium is considered by many mothers to be a safe and innocuous sedative, but, as is well known, it may produce an almost infinite variety of skin eruptions, such as papules, tubercles, vesicles, pustules, bullæ, the lesions being often extensive owing to the eruption becoming confluent.

These and similar complications are not sufficiently common to make them of importance, but the possibility of their occurrence makes it necessary to bear them in mind in making an inquiry into an obscure case of supposed vaccinal eruption.[2]

[1] Cases No. 227, p. 413; No. 309, p. 438; and cf. Cases 198, p. 386; 202, p. 389; and 326, p. 447, *loc. cit.*

[2] For an exhaustive account of drug-eruptions, see P. A. Morrow (42B).

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PART III

VACCINAL INJURIES. ALLEGED AND REAL.

Introduction.—The practice of vaccination has been opposed on three grounds:—(i.) *Theoretical.* It is said that vaccinia and variola are totally distinct diseases, and that the inoculation of cow-pox does not therefore exercise any specific protective power against small-pox (17A). (ii.) *Statistical.* It is stated that so-called cow-pox is nothing else than human variola artificially transmitted; and that statistics of small-pox epidemics demonstrate not only that vaccination does not protect against small-pox, but that it actually causes it.[1] (iii.) *Practical.* It is alleged that the injuries caused by vaccination are so numerous, and so terrible, that there is no justification for the continuance of a practice which may be powerless for good (29A).

This is not the place to discuss the first two propositions, which, if both were true, would be mutually destructive. The third proposition, namely that which relates to the extent and severity of vaccinal injuries, is one which deserves the most careful study. It is alleged that syphilis,

[1] Vogt, Adolf (Bern), *Memorial concerning the Effect of Vaccination.* etc., chap. ii. p. 692, "Identity of Variola, Vaccina, and Variola Vera," chap. viii. p. 707, "Variola Epidemics produced by Vaccine Inoculation." Paper forwarded to the Royal Commission on Vaccination. Appendix to Sixth Report R.C.V. p. 689 *et seq.*

tuberculosis, and other diseases, such as cancer and lupus, have been inoculated at the time of vaccination; and that pyæmia, erysipelas, and various other inflammatory affections result directly from the operation as it is at present performed. Syphilis and tuberculosis have not infrequently been inoculated in the rite of circumcision (20A, 24B), in tattooing (13B), and in other purely accidental ways (13A, 24C). It might therefore seem probable, on *a priori* grounds, that in the practice of vaccination there was real danger to be apprehended from the inoculation of these diseases when the use of humanised lymph was the rule instead of as at the present time the exception. The purpose of the following pages is to inquire how far these allegations are borne out by facts; and, if admitted to be substantially correct, to endeavour to ascertain in what proportion of cases injury was found to occur before the introduction of calf-lymph into general use.

The influence of vaccination on general infantile mortality was epitomised in the Final Report of the Royal Commission on Vaccination, paragraphs 377 and 378, p. 105, in the following passage:—

"Without encumbering our report with the details relating to pyæmia, bronchitis, diarrhœa, and skin diseases, which are all said to have increased owing to the mischievous influence of vaccination, we may confidently say that there is no evidence to justify the statement. It is, however, worth while pointing out, that comparing as before the period 1883-87 with the period 1863-67, the increase of deaths under one year of age from diarrhœa and dysentery in Leicester was 4·2 per cent, whereas in England and Wales it was 0·5 per cent. A similar comparison in respect of bronchitis shews the increase in Leicester to be 112·8 per cent, in England and Wales 73·3 per cent. It seems clear that as regards general infantile mortality Leicester has not gained by its avoidance of vaccination. Whilst in England and Wales the mortality of children under one year of age had between the periods selected for comparison decreased 7·5 per cent, in Leicester the decrease was only 2·8 per cent. Upon the whole, then, we think that the evidence is overwhelming to shew that in the case of some of the diseases referred to, vaccination cannot have produced any effect upon the mortality from them, and that it has not in the case of any one of them increased the mortality to a substantial, we might even say an appreciable extent."

That harm occasionally results from vaccination in individual cases cannot be doubted; but whether the number of cases in which injury is inflicted be large or small, it is interesting to note that the annual infantile death-rate has not increased since vaccination was made compulsory; it has, in fact, diminished. (See Final Report R.C.V. p. 102, para. 385.) The actual numbers are—1838-42, 152 per thousand births; 1847-50, 154; 1851-60, 154; 1861-70, 154; 1871-80, 149; 1881-90, 142; 1891-1900, 154; 1901-4, 140.

It is obvious that these figures give no certain data for determining the actual number of deaths which result directly or indirectly from

vaccination; neither does the diminution in the annual death-rate shew that no deaths result from the operation; but they indicate that no appreciable increase in the death-rate, whether due to vaccination or not, has occurred. There are also other data available for forming a reasonably accurate estimate of the facts.

Statistics of Deaths and Injuries.—The number of deaths or of serious injuries which result annually from vaccination may be arrived at with considerable certainty. From the Registrar-General's returns it appears that in the years 1881-89 the number of deaths certified as connected with vaccination was 476, or nearly 53 a year. During these nine years 6,739,902 primary vaccinations were performed. This gives an average of 1 death to 14,159 primary vaccinations. During the three years from 1st November 1888 to 30th November 1891, 205 alleged cases of injury were inquired into by the medical department of the Local Government Board; and from 1st June 1889 to 1st July 1896, 421 additional cases were investigated by the Royal Commission on Vaccination. Of the cases inquired into by the Local Government Board, Dr. Coupland and I came to the conclusion that in approximately 20 per cent the influence of vaccination was doubtful. Of the cases investigated for the Commission by Sir T. Barlow and myself, about 16 per cent were probably altogether unconnected with vaccination; while of the cases inquired into by Dr. Luff, nearly 40 per cent are placed by him in the same category. As these figures are and can only be taken as an approximation to the actual facts, it is probable that no serious error will be made in supposing that, of the total 626 cases investigated, some 20 per cent may be set aside as unconnected with vaccination; leaving 495 cases of death or vaccinal injury which have been adequately inquired into during the eight years; this gives an annual average of 61·3, or a slightly larger number than that which is arrived at from the Registrar-General's returns, which refer to cases only in which death has occurred. During the four years 1900-3 the average number of deaths certified as due to cow-pox and other effects of vaccination was considerably less, amounting only to 22·5 per annum.[1]

From these statements it will be seen that, however valuable to the community at large, vaccination is not exempt from that liability to accident which exists in all human affairs. Operations of a trivial kind sometimes prove fatal; and even that most beneficent means of alleviating pain which has been universally adopted—the administration of anæsthetics—is not unattended by risk, and occasionally results in death. The percentage number of deaths which occur annually in England from chloroform is far greater than that which results from vaccination. It is, in fact, nearly seven times as great; and though the risk from ether is much less, the percentage number of deaths per annum traceable

[1] During the years 1890-99 (inclusive) the average number of deaths certified yearly as "cow-pox and other effects of vaccination" was 44·7. During the years 1900-3 the average number was only 22·5 yearly. The number of vaccinations during these years was 2,719,664, an average of 1 death to 30,218 primary vaccinations.

directly or indirectly to anæsthetics is appreciably greater than that which follows vaccination,[1] while the total number is approximately the same. It cannot be argued that the rare fatalities attendant upon vaccination are sufficient ground for rejecting the practice if it can be proved beneficial on the whole. If the practice of vaccination is to be rightly discredited, it must be by shewing that the injury thereby inflicted on individuals is out of all proportion to the good which is gained by the community; and not by exaggerating, distorting, and multiplying every isolated instance of injury which occurs. The following pages were written with the object of stating fairly what amount and kind of injury were inflicted by vaccination at a period during which there was a keen desire on the part of those opposed to the practice, to report and have inquiry made into every case in which injury or death was alleged to have resulted from the operation, and with the object of ascertaining how much of it was inevitable, how much preventable, and, by pointing out the dangers, to shew incidentally how many of the risks might be avoided.

In this, as in other branches of pathology, it is incumbent on the medical profession to impose on itself, as a condition of assenting to any doctrine, the obligation of setting forth conscientiously all that can be said against it, no less than all that can be said in its favour.

Erysipelas.—*Relative importance of inflammatory complications.*—Among the complications of vaccination, those are most to be dreaded which are common to all wounds. The most grave are erysipelas, cellulitis, ulceration, abscess, and septicæmia. None of these are peculiar to vaccination; they constitute the dangers of any local lesion of the skin; and, considering the age of the children vaccinated, the conditions under which thousands of them live, and the treatment to which in defiance of the most elementary principles of cleanliness the wounds are often subjected, it is surprising that, as investigation proves, so few cases of serious complications have occurred.

The relative importance of these inflammatory complications may be gathered from the fact that of 205 cases investigated by the Local Government Board,[2] and 189 cases investigated by Sir T. Barlow and myself (11) (all of which have been fully inquired into, and as far as possible placed under definite headings),[3] 133 and 94 respectively come under the category of "inflammatory."[4] In other words, of 394 cases of alleged vaccinal injury recorded during the years 1888-1895 with which

[1] I am indebted to Dr. Childs, secretary of the Anæsthetics Committee, Brit. Med. Association, and to Mr. G. Rowell of Guy's Hospital, for the actual figures, which are as follows:—Deaths from anæsthetics recorded: 1891, 46; 1892, 41; 1893, 46; 1894, 66; 1895, 61: 1896, 8½ months, 48. The deaths from chloroform are roughly 1 in 2000, and from ether 1 in 20,000.

[2] An analysis prepared by Dr. Coupland and Dr. T. D. Acland of the Reports made by Inspectors of the Local Government Board, Appendix ix. to Final Report R.C.V. 1896 (1).

[3] These figures do not give the total number of cases investigated by the medical officers of the Commission, but refer only to those reported on by Sir T. Barlow and myself.

[4] For classification adopted, see Appendix ix. *loc. cit.* p. 2.

I had directly or indirectly to deal, no less than 57·6 per cent resulted from one or other of the specific forms of inflammation. The percentage is almost certainly higher than this; since many of the cases in which the suspicion of invaccinated syphilis has been raised, proved on investigation to be cases of vaccinal ulceration, or some other such lesion; and might properly, therefore, have been included in the inflammatory class. Thus, approximately 60 per cent of all cases of vaccinal injury in this country during the period under consideration were due to some form of inflammation; erysipelas being the most important and of the most frequent occurrence.

To form some estimate of the frequency of post-vaccinal erysipelas over a definite series of years, recourse may be had to the statistical and clinical facts which were laid before the Vaccination Commission (18). It will be seen from the returns of the Registrar-General for Scotland, that during the years (1855-1863) immediately preceding the Act for making vaccination compulsory in Scotland, 28·36 per cent of all deaths from erysipelas occurred during the first six months, and 5·02 per cent in the second six months of life; and that during the years (1864-1887) which immediately followed the passing of the Act, the numbers were 28·88 and 5·35 per cent respectively. This shews conclusively that no new cause, resulting in a different distribution of mortality from erysipelas, came into play in consequence of the passing of the Vaccination Act. Again, the Leicester statistics shew that, comparing the years 1883-1887 (at which time vaccination had largely fallen into abeyance) with the years 1863-67, the infant mortality from erysipelas, which in England and Wales had decreased 16·7 per cent, in Leicester had increased 41·5 per cent. The comparison here made is between Leicester and the whole of England and Wales, a comparison not perhaps strictly exact; but the figures are remarkable, and warrant the conclusion that the neglect of vaccination in Leicester did not at any rate lessen the number of deaths from erysipelas amongst the infant population.

Erysipelas may be defined, according to present knowledge, as an acute specific inflammation of the skin caused by definite micro-organisms, and characterised (i.) by a tendency to spread, mostly by continuity; and (ii.) by a general intoxication running parallel with the local inflammation.

It has been suggested, without adequate proof, that erysipelas following vaccination is "a stage in the evolution of cow-pox"—"a throwing back to one of the original characters of that communicable infection" (14); and that it is "the prime note of vaccination" (31). These hypotheses were anticipated by Bohn, when some thirty years ago he wrote that "the clear, pure lymph of a true Jennerian vesicle possesses the power of engendering erysipelas." It does not admit of doubt that these statements, made in the first two instances with the object of bringing the practice of vaccination into disrepute, are not founded[1] upon any more

[1] It is not of any practical importance whether Jenner thought that the inflammation excited by the cow-pox was "erysipelatous" or not. There is no necessity for limiting the

secure basis than that erysipelas sometimes starts from the vaccination vesicles, as it may start from any wound.

It is possible that the virus of erysipelas has been on very rare occasions introduced with vaccination; but no proof has been brought forward to shew that the vaccine lymph commonly contains this virus, or that erysipelas is a necessary or essential part of vaccination.

Pfeiffer, Crookshank, Landmann (23), Kitasato, Sternberg, Copeman, and others have demonstrated (*a*) organisms capable of producing erysipelas in the vaccine lymph; but they have also shewn that, so far as present knowledge goes, none of these organisms is the specific organism of cow-pox: and (*b*) that vaccine lymph which has been deprived of all known[1] living pyogenetic organisms, still produces the characteristic effects of vaccination (26). It follows from this that complications which result from the presence of the *Streptococcus pyogenes*, *erysipelatis*, or other pathogenetic organisms, are, so far as can at present be stated, accidental, and in no way an integral part of the process of vaccination.

Landmann (24) has shewn that lymph which does not contain any known pathogenetic and but few saprophytic organisms, gives unusually good results when used for vaccination. In forty persons vaccinated with such lymph the areola did not in any case exceed $\frac{3}{8}$ inch in breadth; and Kitasato's experiments led him to the conclusion that the inflammatory symptoms which not infrequently follow vaccination are mainly, if not entirely, due to the presence of extraneous pathogenetic organisms in the lymph. These researches prove—

(i.) That the virus of erysipelas is entirely distinct from the virus of vaccinia, and has no necessary pathological connexion with it.

(ii.) That it is possible to prepare vaccine lymph entirely free from those pathogenetic organisms which are known to excite the specific forms of inflammation.

(iii.) That vaccine lymph freed from all living pyogenetic or saprophytic organisms has not thereby lost its power of producing characteristic vaccine vesicles.[2]

(iv.) That lymph containing the streptococcus of erysipelas may, if the dose be sufficient, excite erysipelas starting from the point of inoculation.

The Incubation-period of Erysipelas.—Much evidence has been adduced from cases in which the initial lesion was known, to shew that this period may be as short as two hours, and possibly in exceptional cases as long as eight days. Thus in thirty-one out of thirty-six cases recorded by

pathological knowledge of to-day by statements made more than 100 years ago (1799). See *Further Observations on the Variolæ Vaccinæ*, by Edward Jenner. Reprinted by E. Crookshank, 1889, p. 187.

[1] As stated in the introduction, p. 666, there is some ground for believing that vaccinia is caused by a specific contagium, although it is not capable of cultivation on ordinary media.

[2] Fürst concluded that the vaccine virus is contained in the living cellular elements, and that no form of bacterium has yet been cultivated outside the body capable of producing definite vaccine pocks. (*Loc. cit.* p. 9, *q.v.* for a summary of the various opinions on this matter.) Also cf. p. 754.

Tillmanns it was three days or less; and in a large majority of cases it was less than sixty hours.

The Length of the Incubation-period of Post-vaccinal Erysipelas seems to correspond with Tillmanns' observations; since, in many cases in which there has been evidence to shew that the lymph was at fault, the erysipelas began at an early period after vaccination; that is, within the limits of time which experimental or accidental inoculation has shewn to be the probable incubation-period of the disease; and it may be stated generally that the sooner after vaccination erysipelas occurs, the more likely it is to have been invaccinated. In a great majority of cases post-vaccinal erysipelas begins during the second week after the operation, at a time when the normal incubation-period of erysipelas has been exceeded, and when, pus having formed at the point of vaccination, there is a ready "nidus" for the reception of any of those wound infections which so frequently follow mechanical injuries resulting in a breach of surface.

Whether erysipelas inoculated at the time of vaccination can remain dormant for days or weeks is a question to which at present no definite answer can be given. Some of the coincidences which have come under my notice are remarkable. For instance, eleven children were vaccinated on the same day (2); in one case only two pocks formed, and on the eighth day this child was revaccinated from one of his co-vaccinees, in two places. Both these children, who lived many miles apart, and as far as I could ascertain never met again, and were not attended by the same doctor, sickened with erysipelas within twenty-four hours of one another about the twenty-sixth day after vaccination, and died within four days of one another, thirty-nine and forty days after vaccination respectively. In another case the vaccinator, apparently ill at the time, died of erysipelas four days after inspecting a child's arm which was inflamed. The child died four days later, also of erysipelas.

In 1891 I undertook a series of experiments on calves and rabbits, with the object of determining (if possible) whether, if the virus of erysipelas be inoculated simultaneously with vaccine lymph, the disease can remain in abeyance until the formation of the pustule on the eighth or ninth day. It is conceivable that with a weak virus in a strongly "refractory" individual the appearance of erysipelas might be delayed until the resistance of the tissues had been overcome by the formation of pus at the point of inoculation; and that a dose of the virus, which in ordinary circumstances would have been inoperative, might then give rise to symptoms, after the normal incubation-period (about three days) of erysipelas had passed. These experiments did not, however, solve the problem completely; the conditions were necessarily so different from those of vaccination that any deductions made from them would require rigorous criticism.

In the numerous cases of post-vaccinal inflammation which I have investigated I have found that, as a rule, when erysipelas occurred more than three or four days after vaccination, it was impossible to obtain adequate proof that it had been invaccinated, or that it was due to the

condition of the instruments used, or to some act on the part of the vaccinator at the time when the operation was performed.

Cases of Vaccinal Erysipelas.—In the following cases of vaccinal erysipelas there is sufficient evidence to justify the conclusion that the lymph or method of vaccination was the actual cause of the disease.

1. Two children were vaccinated with human non-glycerinated lymph stored in tubes; both of them died with symptoms of general diffuse inflammation of the skin which spread over the entire body. In the first child the inflammation was well marked by the third day; in the second child the first vaccination failed entirely, but it was revaccinated from the same source: "soon" after the second vaccination the arm became red and swollen, and by the fourth day the inflammation had spread to the elbow. The tube from which this revaccination was made, and another of the same batch, were examined by Dr. Klein with the following results:—(*a*) The former shewed the presence of numerous colonies of the streptococcus of erysipelas; (*b*) the latter yielded cultures of *Staphylococcus pyogenes albus liquescens.* These cases support the belief that lymph, contaminated with specific organisms in sufficient quantity, may be expected to shew the results of the inoculation of such organisms, whether vaccination be successful or not; and may give rise to local symptoms within a few hours of inoculation, before the vaccine vesicle has had time to arrive at maturity: that is to say, the course of the erysipelas in all probability will not be delayed by the vaccination, but will be the same as if inoculation with the micro-organism had taken place apart from the vaccination (3).

2. Five children were vaccinated with human lymph from the same source (4); in four of these erysipelas subsequently appeared, and one died. The vaccinifer sickened with erysipelas ten days after lymph had been taken from its arm. The cases are noteworthy for several reasons:—(*a*) It will be seen from the following table that the severity of the symptoms varied inversely as the length of the incubation-period. (*b*) All the sub-vaccinees of the vaccinifer (who himself subsequently suffered from erysipelas) did not suffer from erysipelas; one escaped entirely; the others suffered in varying degrees, and the initial symptoms appeared at varying intervals after inoculation.

These gradations in the severity of symptoms, and length of incubation-period, are in harmony with what is known of such factors as dosage, virulence, and receptivity, which determine the effect produced by any given virus.

[TABLE

Case No. 115.

Table shewing date of appearance of erysipelas, etc., in a vaccinifer and four sub-vaccinees.

No. in Register.		First appearance of Erysipelas after Vaccination.	Severity.	Course.	Result.
Vaccinifer—	No. 157, A. S.	17 days	Slight.	Subacute.	Recovery.
Sub-Vaccinees—	No. 166, M. H.	6 hours	Great diffuse swelling; abscesses.	Acute.	Death on 20th day.
Do.	No. 163, B. S.	16 hours	Great diffuse swelling; pyæmia.	Subacute.	Abscesses on scalp, scapula, shoulder-joints, wrists, etc.; not fatal.
Do.	No. 164, F. H.	5 days	Less severe; no suppuration.	Subacute.	Recovery.
Do.	No. 165, T. W.	19 days	Less severe; axillary abscess after 5 weeks.	Chronic.	Recovery.
Do.	No. 167, T. C.	None	...	...	Vaccination normal. Six children successfully vaccinated from this case.

3. In another series of cases there was ground for believing that some infective material had been introduced with the vaccine lymph. Sixteen children were vaccinated: in four of them septic symptoms appeared within 12 hours; in four within 36 hours; in three within 60 hours; in two before the fourth day; in one before the eighth day. Of one there is no record (5).[1]

The following table is of interest as shewing the dates after vaccination at which erysipelas appeared in 100 cases which have been adequately investigated. Of these, ninety-six were inquired into and reported upon by the medical staff of the Local Government Board; the remaining four, added to complete the hundred, were investigated by myself (6). It shews that the great majority of cases occurred at a date after vaccination outside the limits of what is believed to be the normal incubation-period of erysipelas. Only nine cases occurred in the first three days, while no less than ninety-one appeared during the subsequent weeks.

[1] The details of these cases, which were inquired into by Sir T. Barlow and Dr. T. W. Thompson, will be found in Appendix ix. Final Report R.C.V. p. 229: the reports are of such length as to prohibit their introduction here, even in abstract.

No conclusion must be drawn from this table as to the relative frequency of erysipelas after vaccination with glycerinated calf-lymph; since it is impossible to ascertain the total number of vaccinations performed in England with lymph derived from each of the several sources named during the period to which reference is made, which was before the supply of glycerinated lymph was issued to public vaccinators.

TABLE shewing date of appearance in 100 cases of post-vaccinal erysipelas occurring between November 1888 and February 1892.

	Erysipelas occurring in						
	No. of Cases.	First Week.	Second Week.	Third Week.	Fourth Week.	Fifth Week.	Vesicles known to have been opened.
HUMANISED LYMPH							
1. Arm to arm . .	48	First day 3 Fifth day 3 Sixth day 2 Seventh day 4	23	10	1	2	15
2. Tubes . . .	18	Sixth day 1 Seventh day 1	8	7	0	1	3
3. Tubes N.V.E. . .	1	...	1				
4. Points N.V.E. . .	3	Third day 1	2	...	...	...	2
5. Method of preserving not stated . .	6	Second day 1 Fifth day 1	3	1	...	...	1
CALF LYMPH							
1. N.V.E. direct from calf	2	...	2	...	...	...	1
2. Other sources—tubes	6	Second day 1 Sixth day 2	3	...	...	...	1
3. N.V.E. points . .	1	...	1				
4. Conserve—source not stated . . .	1	...	1	...	...	...	1
5. Source and method of preserving doubtful	2	Sixth day 1	1				
SOURCE OF ORIGIN NOT STATED	12	Second day 3 Fourth day 1 Seventh day 4	4				
Totals . .	100	29	49	18	1	3	24

The history of the nine cases in which erysipelas supervened in the first three days is important. In two instances pathogenetic organisms were found in tubes of lymph from the same source as that which had been used to vaccinate the children.[1] In five cases there was strong evidence for believing that the lymph (humanised) was at fault; since more than one child out of each of the three groups of vaccinees (vaccinated on the same day) to which these children belonged suffered from erysipelas; and in each case the vaccinifer suffered from superficial inflammation of the arm. In one case a child was vaccinated with a tube of lymph which had been opened a week previously; another was

[1] Cf. Cases of vaccinal erysipelas, p. 703.

vaccinated when three weeks old, in an infirmary, the bedding on which the mother and child slept having been in a ward in which a case of erysipelas had occurred: the ward had, however, been "fumigated" with sulphur. Thus, in all these cases of early post-vaccinal erysipelas, except possibly the last, there were circumstances which make it probable that the erysipelas was due to some extraneous cause which came into play at or about the time of vaccination.

Such cases might be multiplied; but enough has been said to shew that symptoms may be expected early in those instances in which there is ground for believing that erysipelas, or some septic infection, was introduced at the time of the operation: and, further, that the symptoms may vary greatly in intensity.

It seems probable, if one only of a number of children vaccinated from the same source develop erysipelas later than the fourth or fifth day, that the erysipelas is due to some extraneous cause, and is not invaccinated. On the other hand, if a number of children vaccinated from a common source develop erysipelas before the fourth day, only one or two of the whole batch escaping, the probability is very great that the erysipelas is directly due to the lymph or to some factor introduced at the time of vaccination.

Erysipelas starting from vaccination wounds may be communicated to other persons, as is proved by the records of some of the foundling institutions; notably those of Vienna and St. Petersburg. In the former no less than 31·47 per cent of the deaths was due to erysipelas.[1] Nor is this to be wondered at: the children were vaccinated indiscriminately, the weakly with the strong, often when they were but seven or eight days old. The lymph was collected by the attendants; the vaccine pocks were plastered with zinc powder, until stinking pus exuded from below the scabs (13), and the daily bath was forbidden. Allusion is made to these cases since they have been instanced by a recent writer to shew that "the erysipelas engendered in the process of vaccinal infection, or, in other words, by *exaggeration of the normal areola* and infiltration, may become the source of erysipelatous contagion to others, just as erysipelas of other origins may so become" (15). That erysipelas following vaccination may be communicated to other persons is beyond doubt; but this does not prove that erysipelas is an integral part of vaccination, although it is certain that it frequently follows vaccination when simple and well-known principles of hygiene are disregarded. In the Foundling Hospital at St. Petersburg, after the adoption of such ordinary rules of cleanliness as are essential to the well-being of all infants, especially of the feeble or the very young, the number of cases of erysipelas was reduced by two-thirds.

No attempt has hitherto been made to shew that the areola which forms round healthy vesicles can actually communicate erysipelas to others;

[1] In Würtemberg, during the same time, only one case of post-vaccinal erysipelas was ascertained to have occurred amongst 500,000 children living under ordinary conditions (Fürst, *loc. cit.* p. 69).

or that it contains micro-organisms which are capable of exciting the specific forms of inflammation (16). Even if it be capable of proof that the areola is caused by extraneous pathogenetic bacteria, and not solely by the irritation of the developing pustule, no evidence has yet been adduced that these organisms play any essential part in the process of vaccination. On the contrary, the results obtained with lymph freed from all extraneous bacteria go far to prove that such organisms are not in any way necessary to the production of the specific effects of vaccination.

From Tillmann's experiments, and from clinical observation, it would appear certain that erysipelas need not necessarily start from the point of infection (9). This latter point is of interest as bearing upon the question whether the areola be "erysipelatous." It is certain that erysipelas may occur before the areola is formed, as well as after it has subsided; that it may involve the areola, and subside, leaving the areola still round the vesicles; and that it may occur in a distant part of the body while the areola is still present.

Sources of Danger Independent of the Lymph.—Apart from any intrinsic qualities in the lymph, and independent of all sources of danger from improper methods employed in its collection and storage, there are elements of extraneous and often readily avoidable risk in the circumstances of the infant, and in the method in which the operation is at times performed. For instance, the use, in one case, of a mechanical scarifier which it was practically impossible to clean, and, in another, of ivory points which had frequently been recharged, have come under my observation.

Hypotheses concerning the nature of vaccinal erysipelas which do not take these and such causes into account are likely to be fallacious. The truth is that erysipelas is common in infants, especially as a result of open wounds; and vaccination may act merely as the starting-point for the inflammation.

Vaccinal ulceration and glandular abscess.—Of the other inflammatory complications which have been found to follow vaccination, those of the most frequent occurrence are ulceration at the point of inoculation, and glandular abscess. Nearly 4 per cent of the vaccinal injuries inquired into by the Local Government Board (1888-1891) were due to one or other of these lesions; and in all the cases some extraneous cause was found which might have determined the departure from the normal. An enumeration of some of the many local applications which I have known to be made to the vaccine pocks, and which may well be regarded as the exciting cause of ulceration or suppuration, will be found on p. 727. Disaster on a large scale, in times now long past, has been courted[1] by using as a source of lymph "The shirt sleeve of a patient stiff with purulent discharge from a foul ulcer,"—"Matter found in great plenty on the sleeves of children's shirts,"—"Lymph in one instance taken from vesicles

[1] Creighton, *The Natural History of Cow-pox*, pp. 115-118, *q.v.* for references to the original documents.

on the ninth day; the vaccinifer, three months old and suffering from twelve pocks, being carried from village to village and used to vaccinate 104 children." This list might be extended, but such examples sufficiently shew the ignorance of some persons who have undertaken to perform vaccination; the results—"deep-seated ulcerations and violent inflammations"—being such as might be expected from such disregard of the most elementary laws of hygiene and cleanliness.

I have seen several cases in which ulceration of the pocks, glandular abscesses, erysipelas, and even septic intoxications followed the vaccination (7) of infants whose conditions of life were unfavourable. Amongst these are included illegitimate children born in destitution, and, it may be, vaccinated when a few days old, in a workhouse infirmary: from the comparative comfort of which they are removed before the vaccinated arm is well, to surroundings which could not fail to be harmful even to a healthy child. It is not to be wondered at that such infants, ill-clothed and worse fed, a burden to their mothers, and sometimes with their lives insured, should succumb to an operation even so trivial as vaccination. No mention would be made of such cases here were it not that they have frequently been made the subject of legal inquiry, and the child's death attributed to vaccination. In the majority of cases in which inflammatory complications follow vaccination there are numerous factors which tend to bring about the catastrophe; and it is illogical to draw any definite conclusions as to the origin of the lesion without giving full weight to the extraneous influences which, apart from vaccination, may have been brought to bear upon the individual case. Under the heading Syphilis, p. 727, will be found tables giving the points of difference between vaccinal ulceration and syphilitic chancre; but it may briefly be said here that, as a rule, vaccinal ulceration is well marked at a time when a syphilitic chancre would not yet have developed; and that vaccinal eruptions, if present, differ widely from those which occur as secondary phenomena in acquired syphilis (cf. p. 728). Their development is irregular, their distribution asymmetrical, they are often intensely irritating, and they tend to conform to the various forms of erythema and urticaria rather than to the papular, squamous, and macular eruptions of secondary syphilis.

Gangrene at the point of vaccination.—In isolated cases gangrene occurs at the point of vaccination, and it sometimes follows vaccination in syphilitic subjects. One such case is reported by Balzer; one by Dr. Wheaton. I have myself investigated two cases (8), in one of which the syphilitic parentage of the child was certain and in the other probable. It is not unreasonable to suppose, if the individual vaccinated be the subject of inherited disease, and the operation be performed when the child is very young, that the result is largely due to the condition of the tissues, and not necessarily to any abnormal quality of the lymph. Three cases have been recorded and summarised by Mr. Hutchinson (20) in which there was no known exciting cause for the local lesion except that the child had been vaccinated: it is probable that none of these children

was syphilitic, and it is possible that the phenomena may have been the result of idiosyncrasy in reference to the vaccine virus. Mr. Hutchinson instances, in support of this view, the occurrence of noma and cancrum oris, forms of spreading gangrene which have nothing to do with syphilis, but which may occur as sequels of the acute specific fevers, such as measles or scarlet fever.

Such cases have not infrequently been mistaken for syphilis, and in making the diagnosis it is necessary to bear in mind the natural history and evolution of that disorder. The differential diagnosis will be found on p. 727.

Tetanus[1] may follow as an accidental infection of any wound; as a complication of vaccination it is of the utmost rarity. I am only acquainted with one case in more than five million consecutive vaccinations in this country (cf. Case x., App. ix. R.C.V. p. 6), and even in this one there is no evidence that the tetanus was invaccinated. It has been known to follow vaccination in South Africa in a series of adult natives, who immediately after being vaccinated worked under a tropical sun: and three series of cases in America are referred to by Prof. Woodhead (Vol. I. p. 1042). Such cases require no comment; they only shew that ordinary caution is necessary even in so slight an operation as vaccination.

Other wound infections, such as *osteomyelitis* (24) and *icterus* (?) (20B), are stated to have followed vaccination, nor is this surprising considering the vast number of vaccinated children living in every degree of dirt, destitution, and misery. None of these have come under my own observation; and I am not aware that any cases occurred in the United Kingdom during the ten years 1886-96. So far as the practice of vaccination is concerned they are of no importance; for they only emphasise the fact, which needs no demonstration, that any wound may become septic if the conditions be unfavourable; and that, given an infected wound, the results will depend primarily on the nature of the contamination, and, in a less degree, on the peculiarities of the individual.

General Toxæmia—Nephritis.—It is stated (19) that a general toxæmia may follow vaccination similar to that which occurs in the acute exanthemata, resulting in acute nephritis with the usual evidences of such a condition. These cases are so rare (even if they are not merely a coincidence of an acute nephritis with vaccination) that they are of no practical importance.

Septic infection in relation to various kinds of lymph.—There are no accurate data for determining whether erysipelas and the "septic infections" are more common after the use of untreated calf-lymph, or

[1] *Archives of Dermatology*, 1880, p. 188, contains a reference to a case recorded by Ross, *Southern Clinic*, 1879. vol. i. p. 468. Toms, *Medical News*, 1894, vol. lxiv. p. 209, *q.v.* for reference to five other cases; symptoms of tetanus did not supervene in any of the reported cases within three weeks of vaccination; six out of the seven cases have proved fatal. See also 19C.

humanised lymph; or of lymph stored in tubes, on points, or as a conserve; but it seems certain that glycerinated calf-lymph affords greatly increased security against such inflammatory complications as are due to the lymph itself.

Diffuse inflammation round the pocks in calves is rarely observed. No case had been recorded at the Lamb's Conduit Establishment up to 1897; and Voigt in 1888 had seen one case only amongst 2500 calves; in conjunction with Dr. Carl Menge, I have found that calves are singularly refractory to inoculations of the streptococci of erysipelas, even in association with vaccinia. Our observations, which have been corroborated by Dr. Klein, tend to shew that superficial wounds, such as those caused by vaccination, do not so readily become the starting-point of erysipelas or cellulitis in the calf as in man; and that a virulent culture sufficient to cause abscesses in one species of animal may not produce any evident result in another. These facts are in agreement with the well-known axiom that the effect of any contagion depends not only on the dose and the virulence of the poison, but also on the susceptibility of the individual inoculated.

Reliance must not, however, be placed on the comparative insusceptibility of the calf to erysipelas and septic infections through superficial wounds, to secure the immunity of vaccinated children from erysipelas. Most of the inflammatory sequels of vaccination, if not all, are due to causes which are removable, and therefore, under certain conditions, preventable; the lymph itself rarely contains organisms capable of directly causing erysipelas, and it is probable that all pyogenetic organisms can be removed from lymph, by treating it with glycerin (*vide* p. 761). The result of my own observation leads me to the conclusion that vaccination, performed directly from the calf, is, *cæteris paribus*, followed by greater inflammatory reaction than when humanised lymph is used; but, as stated above, there are no trustworthy figures to shew the percentages of cases of erysipelas or cellulitis which follow vaccination by either method.

In the earlier days of vaccination, when even serious surgical operations were performed with little regard to cleanliness, and when the causes and prevention of sepsis were not understood, the collection, storage, and use of lymph for vaccination were not carried out with the care necessary to prevent contamination with pyogenetic or pathogenetic organisms. But since then the researches of Sternberg, Kitasato, Landmann, Copeman, and other pioneers, have led to improved methods of obtaining and preparing vaccine lymph; and persons having the care of vaccinated children have begun to learn how many of the so-called results of vaccination may be avoided, so that the one complication of vaccination most to be feared, comparatively infrequent as it now is, will, it may reasonably be hoped, except in the rarest instances, be unknown.

The results obtained by Voigt (of Hamburg), whose experience has extended over a period of five-and-twenty years, during which time he

has performed considerably more than a quarter of a million vaccinations, may be taken as fairly representing what is possible. His observations are the more important as he has special arrangements for tracing and investigating every case of vaccinal complication. During the five years preceding 1897, out of 100,000 vaccinations, he saw one case of axillary abscess; two of abscess (locality not stated); one of furunculosis; two of erysipelas; and five of vaccinal ulceration, with only one death. But it must not be forgotten that to secure such results nothing may be omitted which can help to make the operation aseptic. There are many possibilities of sepsis from the belly of the calf, the opened tube, the recharged point, the mechanical vaccinator which cannot be or is not sterilised, the hands of the operator, and the infant's surroundings. These dangers should not occur if the Local Government Board instructions to public vaccinators are loyally carried out; but no vaccinator can afford to run unnecessary risks even in so simple an operation as vaccination. There is no ground for believing that the septic complications of vaccination are "stages in the evolution of cow-pox," or "throwings back to its original characters"; but there is much evidence to shew that the methods employed for the production, storage, and use of lymph are of fundamental importance in the attempt to reach that perfection of asepsis[1] which is necessary in any surgical operation, however small, and which is especially necessary in the case of very young children. From what has been said above it is hardly necessary again to emphasise the importance of giving to every legally qualified practitioner an equal right to a supply of lymph prepared in laboratories at the expense of the State under the best possible conditions, and that the indiscriminate importation of lymph of unknown origin from foreign sources should no longer be permitted.

[1] The question of bacterium-free vaccine lymph was discussed at the 68th Versamml. Gesellschaft Deutscher Naturforscher und Aertze zu Frankfurt a. M. Sept. 1896. Cf. also Neidhart. *Hygienische Rundschau*, No. 21, 1896, p. 1073, and *Chemiker Zeitung*, Oct. 1896, p. 788.

AUTHORS REFERRED TO IN PART III. ON VACCINAL INJURIES

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PART IV

VACCINATION AND SYPHILIS[1]

Introduction.—No part of the study of vaccination is more serious or more surrounded with difficulty than the attempt to estimate at their true value the conflicting statements concerning the transmission of syphilis by this operation. It is, no doubt, true that the invaccination of syphilis is possible; but the facts brought before the Royal Commission (1889-1896) prove that, in England at any rate, the event is one of great rarity, and they do not justify any real objection to the practice of vaccination.

Two methods, the statistical and the clinical, have been adopted to estimate the number of cases of vaccinal syphilis which actually occur. Of these the former is the less satisfactory, since it is liable to many sources of error; and although such figures as are available go far to prove that infantile syphilis has not been increased by vaccination, there is still stronger evidence against its frequency, in the fact that, although every

[1] Since the issue of the Final Report of the R.C.V. in 1896, the use of glycerinated calf-lymph has become general throughout England and Wales owing to the fact that it is supplied to all public vaccinators, and a minority only of vaccinations are performed by private practitioners with lymph of various other kinds. The danger of the invaccination of syphilis, tuberculosis, or leprosy in such circumstances is so remote that, except for historical reasons, this present section might have been omitted. It is, however, desirable that the facts as far as they are ascertainable should be widely known by all who are interested in vaccination; so that with some few necessary corrections the article has been allowed to stand as it was written.

alleged case of invaccinated syphilis brought before the Commission which had occurred between the years 1889 and 1896 was subjected to a searching inquiry, not one of them stood the test of an investigation into all the circumstances. During the years specified approximately five and a quarter million primary vaccinations were performed in the United Kingdom.

Of the cases vaccinated in 1889, and previous to this date, which were inquired into, one [1] was believed by Mr. Hutchinson and Sir T. Barlow not to be a case of syphilis at all. In another (No. 141, App. ix. R.C.V.) the evidence was so indefinite that Sir T. Barlow and I came to the conclusion that though there was some ground for the allegation, it was incapable of proof. This child had been vaccinated in 1880, twelve years before the inquiry was made; but at the time of the investigation there was no evidence of syphilis, invaccinated or otherwise acquired. Only three other cases were brought directly before the Commission in which there was prima facie ground for suspecting that syphilis had been communicated by vaccination,[2] but two of these had occurred twenty-five years previously. [Cf. also table, p. 717.]

If further evidence as to the rarity of the disease be needed, it may be noted that amongst 30,000 patients at the Hospital for Sick Children, Great Ormond Street, where if such cases were of common occurrence they would be met with, Dr. Robert Lee saw only one instance of supposed vaccinal syphilis; while at the East London Hospital for Children, Dr. Radcliffe Crocker had not seen or heard of one such case, although for many years he was making special inquiries as to their occurrence.

Statistical method of inquiry.—During the twenty years preceding 1896 the number of deaths in England and Wales "registered" as due to syphilis had increased: [3] it was suggested that this increase was due to syphilis inoculated at the time of vaccination.[4] The limit of age at which vaccination must be performed in this division of the United Kingdom, was then three, instead of, as at present, six months. As a matter of general experience vaccination was delayed as long as possible, so that any increase in the number of deaths from syphilis due to the operation would probably have occurred in children more than three months old. Such, however, was not the case, the disease was most largely fatal during the first three months of life; so that whatever was the cause of this increase of syphilis, there is no evidence to shew that it was due to vaccination.

In Scotland, where the age-limit is six months, during the period 1855-1863, which immediately preceded that of compulsory vaccination, out of every 1000 deaths at all ages registered as from syphilis, 575

[1] See Case No. 1 of the Commission series, and Case 90, L.G.B. series, Appendix ix. R.C.V.; also Hutchinson's *Archives of Surgery*, vol. i. No. 2, 1889, pp. 106 and 112.

[2] See Final Report R.C.V. pp. 110-114, and par. 424, p. 111.

[3] Final Report R.C.V. p. 103.

[4] Cf. also *Cow-pox and Vaccinal Syphilis*, by Charles Creighton, p. 115, London, 1887, where the increase is attributed, not to syphilis inoculated with vaccination, but directly to vaccination itself, the results being erroneously called syphilis.

occurred during the first six months of life, and 109 between the ages of six and twelve months. During the period 1864-1875 the number of deaths registered as from syphilis during the first six months was 612; and in the period 1875-1887 it was 647. During the same periods the proportions of deaths registered as from syphilis between the ages of six and twelve months were 118 and 109 respectively. Thus in Scotland the number of deaths from this cause occurring during the second six months of life, when the results of vaccination would be most likely to declare themselves, shewed no increase after vaccination had been made compulsory; whilst at the same time the deaths registered as from syphilis during the months preceding the age-limit for vaccination had increased.[1]

In Ireland the number of deaths from infantile syphilis has largely diminished during recent years. In 1864-1865 the average number of deaths so registered was 124; in 1887-1888 it was only 40.

In Leicester, where the practice of vaccination had fallen largely into disuse, the deaths registered as from infantile syphilis for the years 1883-1887 shewed an increase of 69·3 per cent as compared with an increase of only 24·7 per cent for the whole of England and Wales for the same period. It need hardly be said that this increase is in no way connected with the disuse of the practice of vaccination; but it shews that the neglect of vaccination in Leicester has not been followed by any diminution in the number of deaths from infantile syphilis.

For the sake of comparison attention may be directed to the German statistics, from which it would appear that no case of vaccinal syphilis was recorded during the years 1889-1893 amongst a total of twelve and a quarter million vaccinations and revaccinations (30, 35), in the great majority of which "calf" lymph was used.

Whatever percentage of error is to be allowed in these statistics, the above figures emphasise the fact, which, as will be seen, may also fairly be deduced from clinical experience, that the risk of inoculation of syphilis with vaccination is incalculably small.

Clinical method of inquiry.—Turning now to the clinical aspect of the inquiry, it is necessary to distinguish accurately between actual and alleged cases of vaccinal syphilis.

That many of the recorded cases are not syphilitic there can be little doubt. This may be said more especially of those which occurred in the early part of the nineteenth century; but even at the present time cases are reported as vaccinal syphilis which, upon careful examination, do not appear to be of this nature (27). In those cases which I have had the opportunity of investigating, I hesitated to believe that the lesions found originated in vaccination alone. They generally shewed wide divergences from those cases of invaccinated syphilis of which the nature was beyond question, and which have been studied by trained observers. Almost without exception some extraneous factor was present in every case, which

[1] Final Report R.C.V. pp. 101, 102. The statistics are given on the authority of the Superintendent of Statistics in the office of the Registrar-General for Scotland.

determined the character of the phenomena that followed the operation. In some instances there was evidence of culpable negligence of those simple precautions without which no operation is justifiable, and without which any surgical procedure such as vaccination may well be followed by disaster (5, 32).

I did not obtain sufficient evidence in the course of my inquiries to lead to the conclusion that certain rare cases to which reference is here made are reversions to an original type of vaccinia; they appear rather to be abnormal results occurring in the course of a definite affection, such as sometimes complicate any of the acute specific fevers.

To illustrate these cases I would specially refer to (*a*) Mr. Hutchinson's paper on three fatal cases of gangrenous ulceration of the arm after vaccination (20); (*b*) case of simulated vaccination syphilis (21); (*c*) the various cases included under Section D in the Abstract of Reports by Inspectors of the Local Government Board, made by myself and Dr. Coupland; (*d*) Cases 52, 94, 109, 113, 195, 202, reported by myself; (*e*) series 139, investigated first by myself alone, and subsequently with Sir T. Barlow; (*f*) finally, to the "Leeds Case," No. 1 of the Commission's series, probably the most important of all.[1] These are given in full in Appendix ix. to the Final Report of the Royal Commission on Vaccination, 1896. From these reports it will be seen that although in each case the invaccination of syphilis has been alleged, and, as in the Leeds case, the allegation has been stoutly defended, yet the conclusion arrived at, after carefully weighing all the facts that can be elicited, is that none of them was due to this infection. It was found that some were cases of gangrenous ulceration, some the result of vaccination in children suffering from congenital syphilis; and, whatever the origin of the lesion, each individual case presented facts which seemed to be incompatible with the view that the symptoms were those of syphilis inoculated at the time of the operation. The manifestations of syphilis are protean; and in doubtful cases no safe deduction can be made from isolated symptoms. Before any conclusion can be drawn as to the true nature of the disease, it is essential to take into consideration the complete history of the case, its evolution, the date of appearance, and the kind of lesions produced. It cannot be doubted that neglect of such precautions has led in many instances to confusion and to mistaken diagnosis. Amongst the cases inquired into by myself, I have found that the formation of a sore at the point of inoculation a week after vaccination, "appearing rather to be syphilitic than vaccinal," the occurrence of periosteal swellings which arose a week after vaccination in a case unquestionably septic, the occurrence of cutaneous eruptions presenting "a certain suspicion of syphilis" during the second and third weeks,—have each in their turn been taken as evidence of invaccinated syphilis, without regard to the fact that a particular symptom isolated from all others is of small weight in deciding the true nature of a given case. Further, such symptoms become of even less value as evidence when they have appeared "untimely"—that is, at a moment

[1] Cf. also Hutchinson, *Archives of Surgery*, 1889, p. 112.

when, from what we know of the natural history of the disease, the initial sore of syphilis would not have arrived at maturity, and at a period when neither secondary nor tertiary symptoms could have had time to declare themselves. Cases shewing the difficulty of eliminating such sources of error will be found in Mr. Hutchinson's *Archives of Surgery*, vol. i. p. 97, and in the reports by myself to the Royal Commission on Vaccination, Nos. 109, 113, 207, 416, and others. It would not be possible here to enter into these cases in detail.

In his evidence before the Commission (Sixth Report R.C.V. 1895, p. 159, Q. 21,854), Mr. H. H. Taylor put forward the following table of "alleged cases of vaccinal syphilis," at the same time expressing the opinion that it is impossible in many of them to say whether "the signs which followed vaccination were the manifestations of syphilis or cow-pox."

This table is too untrustworthy to be of any service in estimating the actual number of cases of vaccinal syphilis which occurred during the years specified; but it is important as shewing the extreme difficulty of obtaining accurate information on the subject.

The danger of drawing any conclusion from it is well illustrated by the fact that, although Mr. Taylor handed it in as a table of *alleged* cases of vaccinal syphilis, Dr. (now Sir W.) Collins and Mr. Picton (4) allude to it as a list of cases of vaccino-syphilis; and both Mr. Taylor and Dr. Creighton use these same cases as evidence that the so-called vaccinal syphilis is nothing but cow-pox. No further testimony is needed to shew the inextricable confusion of the whole subject.

[TABLE

English Cases of "Alleged Vaccinal Syphilis," taken from Mr. H. H. Taylor's Table. See Appendix Sixth Report R.C.V. 1895, p. 617. Foreign cases have been omitted.

N.B.—The references given have in some instances been amended.

No.	Date.	Place.	Number of Cases.	Authority.	Remarks, T. D. A.
1.	1802	London	1	Letter from Mr. Smyth Stuart in Squirrell's *Observations on Cow-pox*, 1805, p. 39.	No mention of suspicion of syphilis at place of reference. The words are, "I was led to consider the cow-pox virus possessed a specific scrofulous nature."[1]
2.	1859	Manchester	14	Whitehead, Third Report, Clinical Hospital, Manchester, 1859, p. 51.	Inconclusive. Evidence very meagre. No details given sufficient to exclude congenital disease. No facts given in support of the suspicion raised.
3.	1871	London	21	Hutchinson, *Illustrations of Clinical Surgery*, fascic. vi. pp. 115 and 122.	Recorded by Mr. Hutchinson as cases of vaccinal syphilis—as are also those marked †.
4.	1871	London	1	T. Smith, *Clinical Society's Transactions*, 1871, vol. iv. p. 53.	Probably a case of invaccinated syphilis, but report very incomplete. No mention of vaccinifer nor co-vaccinees.
5.	1872	London	1	Hutchinson, *loc. cit.* p. 126.	†
6.	1873	London	1	Hulke, *Med. Times and Gazette*, 1873, p. 153.	No details. Mr. Hulke said he had seen a case which he believed to be vaccinal syphilis. No facts given in support of the suspicion raised.
7.	1876	London	1	Hutchinson, *loc. cit.* p. 128.	† Should be two cases. Mother contracted syphilis from suckling her child; primary sore on nipple; symptoms followed two months later than in children. Father contracted disease from wife.
8.	1883	London	40	Transactions of the *Vaccination Inquiry.* Edited by M. D. Makuna. Part I. 1883.	Quite unreliable. Sixteen correspondents say they have seen cases, but no details are given.
9.	1883	London	1	Druitt, quoted by H. Lee: Holmes' *System of Surgery*, ed. ii. vol. iii. p. 349.	Case did not occur in England. No details. Dr. Druitt saw the case abroad and made a sketch of it.
10.	1889	London	2	*Archives of Surgery*, vol. i. p. 97.	Recorded by Mr. Hutchinson as not being vaccinal syphilis; although two were thought by some who saw them to have been syphilitic.
11.	1890	,,	3	Do., vol. i. p. 193.	
12.	1891	,,	1	Do., vol. ii. p. 213.	

[1] Creighton, *loc. cit.* p. 113, states that the word "venereal" stood in the original, but was suppressed, and "scrofulous" substituted; the words "suspected venereal taint" appear in

Some further comment is needed on two of the above series, Nos. 2 and 8.

No. 2.—Dr. Whitehead gives a table of sixty-three cases (out of a total of 2584 patients) which he believes to have been syphilitic; and out of this number fourteen are attributed to vaccination. In none of these cases is the condition of the vaccinifer or co-vaccinees mentioned; there is no evidence to shew that they were examined: in three cases only is it definitely stated that the father and mother were healthy, and even as to these, no statement is made that either father or mother was examined. Deductions drawn from such uncertain data must obviously be liable to many fallacies.[1]

No. 8.—This series is useless for accurate purposes, no details are given in Mr. Makuna's Inquiry; sixteen observers say that they have seen cases of invaccinated syphilis (twenty-one cases), but their replies are very inconclusive, and there is nothing to shew which of those who answered Mr. Makuna's "Inquiry" had seen particular cases, or whether more than one of them had seen the same case.

Clinical history of vaccinal syphilis.—The inoculation of syphilis at the time of vaccination may be due to various causes: (i.) To direct contamination of the lymph taken from a vaccinifer suffering at the time from syphilis (9, 28, 35). (ii.) To accidental contamination of the instrument or wound. (iii.) To infection from the vaccinator. It has been suggested (19) that infection might be conveyed by a vaccinator, suffering at the time from syphilis, blowing out the lymph from the capillary tube, but there is no evidence that such an accident has ever taken place.

In whatever way syphilis be invaccinated a certain definite sequence of events may be expected. These are as follows: if the person vaccinated be susceptible to vaccination the pocks may not at first shew any departure from the normal course, but in some cases the pocks abort, and the pathological process seems to be at an end until the syphilitic virus asserts itself. If the pocks be irritated, or the condition of the tissues be such as to favour suppuration, the vaccinal sore may become inflamed, suppuration may occur, and the ulcers may for a time scab over and then break down again; but in any circumstances, whether the vaccination pursue a normal or an abnormal course, a true syphilitic chancre with indurated base eventually forms at the point of inoculation.[2]

Cory's experiments on himself, reported by Bristowe, Hutchinson, Humphry, and Ballard, throw valuable light on the clinical history of invaccinated syphilis; and the sequence of events in vaccinal syphilis

a version of the letter published by Dr. Smyth Stuart two years after Squirrell's *Observations* were published. Cf. *An Address on Vaccination*, etc., by Ferdinand Smyth Stuart, Esq., London, 1807, pp. 9 and 68.

[1] Creighton (5) uses these cases as an argument in support of his view that vaccinal syphilis is not of "venereal" origin at all, but due "to the inherent although mostly dormant natural history characters of cow-pox itself."

[2] Fournier, *loc. cit.* p. 125. Cf. also table on page 721 for further details.

may be studied from this case, which was carefully observed and recorded (33).

R. C. purposely vaccinated himself on four occasions from children known to be syphilitic. On the first occasion, in 1877 or 1878, vaccination was successful, but the vesicles matured early and declined after the fourth or fifth day. No syphilitic trouble followed. Some two years later he vaccinated himself again from a tainted source. Neither vaccinia nor syphilis resulted. About eighteen months later he repeated the experiment, again with negative results. On the fourth occasion he was vaccinated in three places (34), from a child who was selected as being obviously the subject of congenital syphilis. She had suffered from thrush, snuffles, and a cutaneous eruption. At the time the lymph was taken from her arm she had sores on the right buttock and the left nostril; and there was still a cutaneous eruption, though not in the immediate neighbourhood of the vesicles, which were normal and not inflamed: they were shallow, however, and difficult to prick without drawing blood. The lymph was collected on a cleansed lancet, the utmost care being taken to avoid any admixture of blood. The next day the three insertions were red, with small areolas which declined gradually, and the arm was entirely healed in six days. On the twenty-first day a red papule formed at two of the points of inoculation: these slowly enlarged, and on the thirty-first day one began to desquamate. The papules continued to increase in size up to the thirty-fifth day, a slight areola being occasionally visible. On the thirty-fifth day a little yellow spot appeared in the centre of one of the papules, and by the next day a scab had formed over it. Two days later (the thirty-eighth day) the scab which covered this papule was removed, and a small ulcer was found beneath it. On this day the arm was seen by the late Sir George Humphry and by Mr. Hutchinson; both observers considered the lesions to be syphilitic. The diseased parts were then removed with antiseptic precautions, and five days later almost all tenderness had disappeared; but for the first time an enlarged and painless gland was felt in the axilla. Next day, the forty-fifth, the lower wound was indurated, and the punctures caused by the needles, with which the edges of the wound had been united, had sloughed; and increasing pain was felt in the axilla. For the next four days the pain in the axilla was severe, and the glands were enlarged and tender; and on the fiftieth day, the constitutional symptoms having been gradually increasing, there was a distinct feeling of illness. Two days later, blue pill (5 grains daily) was taken with much benefit; but on the fifty-fourth day rheumatic pains were felt, followed within forty-eight hours by much soreness of throat; next day, the fifty-sixth, the cervical glands became painful; on the fifty-seventh day a roseolous eruption appeared on the forehead, the temples, the back of the neck below the ears, and the lower part of the abdomen, which lasted four days; after this date antisyphilitic treatment was fully carried out. The subsequent history of the case shews that the experiment was only too successful.

TABLE giving symptoms and dates in a case of Invaccinated Syphilis (R. C.)

Stage.	Date.	Symptoms.
Primary . .	1st day, July 1, 1881.	Inoculation in 3 places on left forearm.
	8th ,,	Arm healed.
	21st ,,	Papules at points of inoculation.
Secondary .	35th ,,	Earliest appearance of ulceration.
	38th ,,	Chancres of ordinary syphilitic type, at one point of inoculation. Parts inoculated excised.
	44th ,,	Glands first noticed to be enlarging.
	45th ,,	One wound indurated.
	47th ,,	Sore throat.
	54th ,,	Pains in limbs.
	57th ,,	Roseolous eruption lasting four days only.
	88th ,,	Acne chiefly on back.
Tertiary . .	21 weeks.	Indurated mass began to form on left thigh (gumma). This inflamed and broke down.
	23 ,,	Two gummas, and a little later tenderness over the tibia (? periostitis).
	7 months, 1882.	Throat sore, other symptoms better.
	7½ ,,	Headache.
	8 ,,	Acne spots fading, wounds of gummas healing.
	8-13 ,,	Some occipital headache, worse at night. Pupils unequal, right generally the smaller.
	14 ,,	Tingling in right hand. Vertigo. Tingling right foot, intermittent at first, then constant.
	Sept. 17, 1882.	Slight aphasia.
	15½ months.	Loss of power on right side.
	1-2 years.	Symptoms gradually passed away. No evidence of syphilis 2½ years after inoculation.

The deductions which may be made from such a case are important, and bear out what has been frequently observed :—

(*a*) That vaccination can be successfully performed with lymph taken from a source tainted with syphilis without necessarily communicating the disease (10, 37).

(*b*) That if syphilis be communicated in the process of vaccination it does not follow that all the points of insertion will become infected (11).

(*c*) That the evolution of syphilis, as regards the primary and secondary stages, is not *necessarily* disturbed, *i.e.* that it may be neither accelerated nor retarded by simultaneous vaccination (12, 8).

(*d*) That no care in the selection of lymph obviates the risk of vaccinating from an obviously tainted source (13, 7).

(*e*) That when syphilis is communicated by vaccination the first appearance of the disease is at the seat of puncture ; and that there is no evidence of general infection until a much later period.

For the sake of clearness a table of the symptoms of vaccinal syphilis, as they have been generally observed, is given below for comparison with those present in R. C.'s case.

Symptoms of Invaccinated Syphilis.		Symptoms in R. C.'s Case.
1. Chancre	Initial chancre at point of vaccination invariable.	Initial chancre at point of inoculation.
2. Glands	Indolent swelling of glands. Duration of the above prolonged without treatment.	Axillary glands at first enlarged without pain; subsequent pain much relieved by mercury.
3. Evolution	Regular.	Regular.
(*a*) Incubation	No definite effect before the end of 3rd week, usually end of 4th or even 5th (24).	Papule first noticed at end of 3rd week.
(*b*) Chancre	Of ordinary syphilitic form.	Chancre of ordinary syphilitic form.
(*c*) Second incubation	Second incubation-period.	Second incubation-period.
(*d*) Generalisation	Generalisation takes place between the 50th and 70th days; if disease be untreated 6th - 10th week, Hutchinson,[1] 9th - 10th, Fournier (15).	Rheumatic pains on 54th day, roseolous eruption on 57th day.
4. Eruption	At first roseolous, generally on abdomen. Subsequently polymorphic, symmetrical. Infrequent on hands and face (25), except in severe cases. Condylomas at junctions of mucous surfaces, common.[2]	At first roseolous on abdomen, forehead, temples, neck.

For further details and for tertiary symptoms see table p. 720.

As care is almost universally exercised in the selection of lymph there is little danger of producing such aberrant results as are seen when pus is inoculated at the same time as the syphilitic virus. In such cases the initial symptoms may be perplexing, and the true nature of the lesion may be only detected during the subsequent history of the case.

Various important questions arise in the consideration of cases of vaccinal syphilis.

i. Is it necessary that, as in the case of R. C., the vaccinifer should be obviously syphilitic; or can the virus be communicated from a child apparently in good health?

ii. What is the actual vehicle by which the virus is transmitted?

iii. Given a healthy vaccinifer, can syphilis be communicated in the act of vaccination independently of the lymph?

[1] *Syphilis*, by Jonathan Hutchinson, 1889, p. 114, if without treatment 6-10 weeks, if treated with mercury 5-7 months; cf. also *Illustrations of Clinical Surgery* (by the same author), London, 1877, p. 133.

[2] For illustrations of invaccinated syphilis see *Illustrations of Clinical Surgery*, by Jonathan Hutchinson, London, 1877, plates xxii. xxiii. xxiv., and *Syphilis*, by the same author, plate iii. p. 104; also cf. Fig. 12, p. 615.

iv. Can syphilis be communicated in lymph taken directly from the calf?

(i.) As regards the first proposition, none of the recorded cases seem to me to prove beyond doubt that a child not in the active stage of syphilitic infection can communicate the disease; though Fournier (16) and others appear to think that it is possible. Mr. Hutchinson's cases (23, 29) have been accepted as evidence on this point; but it is possible that the infection may have been conveyed by the lancet from another child, and not from the vaccinifer at all. With regard to this point it is important to remember that, as has been stated (cf. p. 693), vaccination may pursue a typically normal course in a syphilitic child provided that it is not cachectic.

(ii.) The question of the actual vehicle by which the virus is transmitted has long been under discussion. Viennois (de Lyon) was of opinion that the virus is contained in the blood. It has been asserted by Barthelemy,[1] and later by Husband,[2] that it is practically impossible to collect lymph in the ordinary way which does not contain blood-corpuscles; so that, if collected from vesicles on a syphilitic individual, apparent clearness of the lymph is no security (cf. Deduction, *d*, p. 720).

(iii.) The following cases have been mentioned by Voigt as supporting the view that syphilitic infection may be communicated from a child's co-vaccinees.

At Tauberbischoffsheim four children were vaccinated from an infant whose mother was a woman of the town: this child died shortly after being used as a vaccinifer. All four sub-vaccinees subsequently presented symptoms of syphilis; three were probably of syphilitic parentage, and inasmuch as the vaccinifer at the time the lymph was taken from its arm is said to have shewn no sign of congenital disease, it is suggested that the fourth was infected from one of its co-vaccinees (1). The evidence is very inconclusive; especially as the physician, under whose care the vaccinifer was when he died, suspected some inherited taint. The vaccinifer seems to have been selected without regard to the ordinary precautions which should invariably be taken in every instance. Such instances shew the importance in all cases of suspected vaccinal syphilis of investigating the history of the co-vaccinees, and of the vaccinifers in the direct line, for some generations; lack of information on these points must invalidate any deductions subsequently made as to the source of infection.

(iv.) It is probably impossible for syphilis to be conveyed by lymph taken directly from the calf, even though the calf had been vaccinated from a syphilitic child; it has been shewn by Koch that the syphilitic poison is destroyed by passing through the animal, and there is no evidence to shew that cattle are susceptible to this disease (18). The foregoing statement shews from clinical evidence that although it is possible to transmit syphilis in the act of vaccination, it is of very rare occurrence, and is not to be feared if ordinary precautions are taken.

[1] Fournier, *loc. cit.* p. 112.
[2] Final Report R.C.V. 1896, p. 112, para. 430.

The disease is stated to have been transmitted from a syphilitic vaccinifer in some fifty series of cases during the last century (26). Even if this estimate be approximately correct, it shews that amongst the many millions of vaccinations, the danger to an individual of contracting syphilis through the operation is inappreciable; and that such indeed is the fact is borne out by a statement made by Mr. Hutchinson to me some little time ago that he had not seen a case of vaccinal syphilis for ten years —evidence as to its rarity more convincing than a multitude of statistics.

Differential diagnosis of vaccinal syphilis.—It remains to call attention (i.) to the main differences which have been found to exist between vaccinal syphilis and other lesions following vaccination; (ii.) to the points which may lead to the correct differentiation between invaccinated syphilis and vaccinia occurring in a syphilitic child; and, lastly, (iii.) to the points of difference between vaccinal ulceration and vaccinal chancre.

(i.) *The differences between vaccinal syphilis and other lesions which may follow vaccination* are well illustrated by the Leeds case,[1] which has been alluded to more than once. In this instance the child when vaccinated was nearly four months old. She was the third in the family, was at the time in good health, and had been previously so. The parents, the vaccinifer, and the co-vaccinees, so far as could be ascertained, were all healthy and without any signs of syphilis. On the sixth day some inflamed spots formed at the seat of inoculation; the inflammation spread rapidly, and towards the end of a fortnight two deep ulcers had formed with much dusky swelling round them. The inflammation and ulceration spread, and at the end of the month the child seemed ill. There was some false membrane on the velum and tonsils, and aphthæ appeared in the mouth; subsequently an ulcer formed on the upper eyelid, and one over the ear on the same side as the vaccination. Nine and a half weeks after the operation all the points of insertion had sloughed into one, producing a large unhealthy ulcer; and the two sores mentioned above were phagedenic. Nothing abnormal was noted in the mucous membrane of the mouth, and neither then nor subsequently was there any general eruption. The child's nutrition was fairly good. The child was treated with mercury, under the impression that it was syphilitic, and the lesion seemed to improve. The sores on the eyelid and ear almost healed, but that on the arm remained unaltered, and "the mouth became very sore." About three weeks later the child was much worse, a large abscess formed on the right buttock and another over the upper part of the sternum. The skin over these parts was implicated, and appeared about to slough. Death resulted at the end of the fourteenth week after vaccination. The post-mortem examination did not throw any light on the nature of the case. No lesions of the viscera or bones were discovered. The arguments against the view that this was a case of invaccinated syphilis are:—

[1] Case I., Appendix ix. to Final Report of Royal Commission on Vaccination; and evidence of Mr. Ward, Mr. Littlewood, and Dr. Barrs, Sixth Report of the R.C.V., Questions 23. 574-912; and Report by Mr. Hutchinson, *Archives of Surgery*, vol. i. p. 106.

(*a*) That the vaccine punctures began to inflame within a week; (*b*) that they did not develop into chancres; (*c*) that they did not cause any induration of glands; (*d*) that there was no general secondary eruption; (*e*) that the mother suckled the child and did not contract any sore upon the nipple; (*f*) that the chronology of events was quite unlike that of vaccinal syphilis; (*g*) that there was no evidence of syphilis in the vaccinifer; (*h*) that none of the co-vaccinees suffered in a similar way.

In view of all these negative data, the only satisfactory way of demonstrating that such a case was one of invaccinated syphilis would be to shew that there was a probability of contamination of the lymph or of the instruments used in the operation. No evidence of this kind was to be obtained; so that the conclusion is justified that these, and similar cases, are erratic forms of necrosis following vaccinia, and are possibly due to sepsis, thus resembling cancrum oris or noma which sometimes follow acute febrile diseases, such as measles and varicella, without giving any ground for suspecting a syphilitic infection.

In the following table the events in the case referred to are given side by side with those to be looked for in a case of vaccinal syphilis, as given by Fournier, *loc. cit.* p. 126:—

	Vaccinal Syphilis	E. M. C. Leeds Case.
Incubation .	Chancre never formed before 15th day, generally after 3 weeks. (Usually end of 4th or even 5th week—Hutchinson.)	First sign of inflammation on 6th day. Ulcers formed during 2nd week.
Development	By the 21st day ulceration in its earliest development, or not yet commenced.	Ulcers fully formed by 14th day.
Vesicles .	As a rule all the vesicles are not affected, vaccination often aborts.	All the vesicles affected.
Inflammation	As a rule slight.	Great.
Loss of substance	Loss of substance superficial as a rule. Cf. Hutchinson, *Illustrations of Clinical Surgery*, 1878, pp. 121, 131.	Great. Vesicles sloughed into one large ulcer.
Discharge .	Scanty as a rule or absent. Generally forming scabs.	Considerable. Not drying into scabs.
Glands .	Enlargement always present, generally indolent, non-inflammatory induration.	No induration of glands.
Secondary eruption	Roseolous eruption frequently present after formation of chancre, followed, at earliest, 6 weeks later, by true syphilides.	None.
Tertiary symptoms	Gummas not generally present for many months after primary sore.	Large abscesses formed, surmised to be softening gummas, 12 weeks after vaccination.
History .	A history of syphilis in parents, vaccinifer, or co-vaccinees to be expected.	No history of syphilis in vaccinifer or co-vaccinees.

(ii.) *The differential diagnosis between vaccinal syphilis and the results of vaccination in a syphilitic child* in cases in which vaccination is either normal or abortive does not, as a rule, present any serious difficulty. But in those cases in which pus has been inoculated with the specific virus, or the pocks have been irritated and suppuration consequently set up, there may be some departure from the normal course of events.

I have recorded several important cases of this kind. In one the mother of the child had suffered severely from syphilis, and she had already lost one child from congenital disease. Her infant suffered after vaccination from severe inflammation round the pocks, which resulted in gangrene (see Case 202, App. ix. to final Report R.C.V.). In another instance a child exhibited a general eruption during the first week after vaccination, and was shewn at a London hospital two days later as a typical case of congenital syphilis: there was evidence that both parents had suffered from venereal disease (Case 326, App. ix. R.C.V.). Lastly, attention may be directed to Case 309, wherein, so far as can be ascertained, the vaccination pursued a normal course, and the child died with symptoms of inherited disease; whilst the history of the parents gave strong support to the view that this diagnosis was correct.

The chronological order and sequence of events in these or similar cases may be seen in the following table compiled from Fournier, Hutchinson, and others, and compared with a case investigated by myself:—

Symptoms and Sequence of Events.	Hereditary Syphilis.	H. C. Report No. 207, p. 397.
Evolution .	Irregular. Commencing as a rule with general symptoms.	Irregular. Ulcer at seat of vaccination formed by 12th day. No induration of base. Ulcer healed in 6 weeks without specific treatment. Evidence of general infection at the end of 5th week.[1]
Rash . .	Rash papular and pustular, often chiefly on face. Roseola on abdomen not the rule. Rash and excoriation round nates and scrotum common.	Rash papular and pustular, chiefly on face, chest, and arms. Not preceded by any roseola on abdomen.
History .	Family history of syphilis important.	Grounds for suspecting syphilitic infection in both father and mother.
	It is almost unknown for a child suffering from hereditary syphilis to inoculate its mother.	Mother suckled child without infecting her nipple.

(iii.) *Differences between Vaccinal Ulceration and Vaccinal Chancre.*—Allusion has been frequently made to vaccinal ulceration; and though

[1] Compare with table of symptoms in vaccinal syphilis on pp. 727-729.

Fig. 18.—Vaccinal ulceration. From a photograph taken in the 2nd week after vaccination.

Fig. 19.—Vaccinal Syphilis. Reproduced from a drawing of Mr. Hutchinson's case, *Illustrations of Clinical Surgery*, plate xxiv. Three chancres are situated at the point of vaccination. The vaccinal pocks went through their normal stages and healed well before the chancres developed. The drawing was made two months after vaccination, when induration was just commencing.

unquestionably it appears to occur at times in children not obviously cachectic, my own experience has been that it is mostly the result of some morbid condition — as in Case 202, in which the child was unquestionably of syphilitic parentage; or of some extraneous source of irritation—as in Case 144, where the wounds were treated with castor oil, with buttermilk applied with a feather, with brewer's yeast, and with bread poultices. It is in fact wonderful that severe ulceration does not more frequently occur. I have been shewn a case with ulceration, considered suggestive of syphilis, in which the wounds had been treated with cream applied with a feather which was picked up in the back yard and which had been left unwashed in the cream for some weeks. In another case buttermilk was applied to a piece of rag and left adherent to the wounds for some three weeks without being changed. I have also seen cases in which the vaccination wounds had been scrubbed and irritated by the edge of the sleeve saturated with the pus and blood in which it had been soaked for many days. These instances might be multiplied; but those given sufficiently indicate the fallacies which beset the opinion that cases of vaccinal ulceration taken without knowing the circumstances are either suggestive of syphilis, or "are manifestations of cow-pox," or necessarily indicate any analogy between the two disorders.

The ordinary features of vaccinal ulceration (Fig. 18) are shewn briefly in the following table taken from an actual case, and placed side by side with those usually observed (17) in vaccinal syphilis (Fig. 19):—

TABLE comparing Vaccinal Ulceration and Vaccinal Syphilis, with an actual case (see Figs. 18 and 19).

Generally observed Symptoms of Vaccinal Ulceration.		Case of J. W. P.	Vaccinal Syphilis.
	1. THE ULCER		
Incubation .	12 to 15 days.	14 to 16 days.	Generally upwards of three weeks, never less than 15 days.
Development .	Ulceration fully developed by 21st day.	Ulceration well marked by 16th day, at its height on the 25th day.	Ulceration in its earliest development, or not yet commenced, about 21st day.
Vesicles affected	As a rule all vesicles affected.	All the vesicles (three) affected according to Dr. H. V.; one ulcer formed according to Mrs. P. the mother.	As a rule all vesicles not affected. Vaccination vesicles often abort.
Inflammation .	Generally prominent.	Considerable.	As a rule slight.

TABLE comparing Vaccinal Ulceration and Vaccinal Syphilis—*continued.*

Generally observed Symptoms of Vaccinal Ulceration.		Case of J. W. P.	Vaccinal Syphilis.
	1. THE ULCER		
Loss of substance	Great. Ulcer generally deeply excavated.	Great. Ulcer deeply excavated.	Loss of substance, superficial with rare exceptions. Much less excavated than a vaccinal ulcer. (Compare a case which was "probably on the verge of phagedæna," *Illustrations of Clinical Surgery*, Jonathan Hutchinson, 1878, at pages 126 and 131.)
Discharge .	Considerable; not drying into scabs.	Considerable; not drying into scabs.	Scanty or absent, nearly always forming scabs.
Edges . .	Punched out, perpendicular, irregular.	Punched out.	Not punched out, sloping to floor.
Bottom . .	Uneven, unhealthy-looking, sometimes sloughy.	Unhealthy-looking.	Smooth, even.
Base . .	Inflammatory induration.	Inflammatory induration.	Induration circumscribed, elastic, parchment-like.
Areola . .	Extensive. Diffuse inflammation, lymphangitis, cellulitis, erysipelas, and other inflammatory complications common.	...	Very slight, often inappreciable.
	2. THE GLANDS		
Glands . .	Either no reaction or acute inflammation.	Not noticed to be enlarged.	Enlargement always present, indolent non-inflammatory induration.
	3. THE ERUPTION		
Development .	First appearance between the 9th and 15th days, always contemporaneous with vaccination.	First rash, red with some exudation noticed on 10th day after vaccination. Second rash, scaly, coppery, about 40th day.	At the earliest, appears first, 63 to 70 days after vaccination. (In Mr. Hutchinson's cases it varied from 42 to 63 days when untreated, and from five to seven months in those under mercurial treatment. (*Loc. cit.* p. 133.)

TABLE comparing Vaccinal Ulceration and Vaccinal Syphilis—*continued.*

	Generally observed Symptoms of Vaccinal Ulceration.	Case of J. W. P.	Vaccinal Syphilis.
3. THE ERUPTION			
Relation to primary sore.	Not preceded by a typical vaccinal chancre.	Not preceded by a typical vaccinal chancre.	Always preceded by a chancre at the point of vaccination.
Clinical characters.	Of ordinary types (roseola, miliaria, bullæ, etc.); not lasting. No mucous tubercles.	No mucous tubercles.	Characteristic syphilides; persistent. Mucous tubercles often present.

Some further points of distinction between vaccinal and syphilitic eruptions will be found in detail on p. 675.

What I have stated above will have indicated some of the many sources of fallacy which have to be guarded against in the investigation of an alleged case of vaccinal syphilis; and the section on this subject cannot be better brought to a conclusion than by quoting the judicial statement made in the Final Report of the Royal Commission, 1896, paragraph 423, which is as follows:—

"The close resemblance in certain very rare cases of the results of vaccination, whether with calf lymph or humanised lymph, to those attributed to syphilis (a resemblance so close that it has caused in a few cases a difference of opinion whether the disease was syphilis or vaccinia), has led to the expression by Dr. Creighton of the opinion that there is some essential relationship between these two diseases. This, however, is a point of speculation, almost it might be said of transcendental pathology, upon which for practical purposes it is useless to enter. It must be sufficient to remark that, whatever may be the relationship alluded to, it exists, if it exist at all, equally between small-pox and syphilis as between vaccination and syphilis. For all practical purposes variola and vaccinia are both wholly distinct from syphilis, and their differences are, with the rarest exceptions, easily recognised. They are alike in being attended by affections of the skin and mucous membranes, and exceptionally by disease of the bones, eyes, and other parts, but in all these it is a question of resemblance and not of identity with which we have to deal."

REFERENCES TO PART IV. ON VACCINAL SYPHILIS

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proposition 1; p. 112, note.—12. *Ibid.* p. 59.—13. *Ibid.* p. 116, propositions 1, 3.—14. *Ibid.* p. 150.—15. *Ibid.* p. 132.—16. *Ibid.* p. 98.—17. *Ibid.* p. 126.—18. Fürst. *Pathologie der Schutzpocken-Impfung*, 1896, p. 56.—19. Hausmann. *Berl. klin. Wchnschr.* 1885, No. 15.—20. Hutchinson. *Archives of Surgery*, 1889, p. 97.—21. *Ibid.* p. 122.—22. *Idem. Illustrations of Clinical Surgery*, 1878, p. 114.—23. *Ibid.* p. 122.—24. *Idem. Syphilis*, p. 108.—25. *Ibid.* p. 148.—26. Lotz. *Variole et vaccine*, p. 112. Bâle, 1880.—27. *Med. Times and Gaz.*, London, May 17, 1873.—28. *Med. stat. Mittheil. a. d. K. Gesundheitsamte*, 1886.—29. *Med.-Chir. Trans.*, London, 1873, pp. 193, 196.—30. *Medizinal statistische Mittheilungen aus dem Kaiserlichen Gesundheitsamte*, Bd. i. ii. iii. Berlin, 1892-1896.—31. Peiper. *Schutzpocken-Impfung*, Wien, 1892, 9, 62.—32. Seaton. *Handbook of Vaccination*, chap. xiv. p. 320. London, 1868.—33. *Supplement to 12th Annual Report of the Local Government Board*, 1882, p. 45.—34. *Ibid.* p. 46.—35. Voigt, L. "Ueber Impfschäden," *Deutsche med. Wchnschr.* 1888, p. 890.—36. *Ibid.* p. 933.—37. Viennois. "De la transmission de la syphilis par la vaccination," *Arch. gén. de méd.* 1860, and "La syphilis vaccinale," *Gaz. hebd. de méd. et de chir.* 1865.—38. Whitehead, James. *Third Report of the Clinical Hospital, Manchester*, p. 51. London, 1859.

Part V

Vaccination in Relation to various Diseases

Vaccination and tuberculosis. — The question of the possibility of the transmission of tuberculosis by vaccination has received much attention. Degive stated that it had been proved that the vaccine pustule could transmit tubercle; but no evidence was brought forward at the time in support of the assertion. When traced to its origin it was found to rest on an account given by Butel of some experiments performed by three Greek physicians, and on some well-known experiments made by Toussaint;[1] and not on any new facts brought to light by the speaker. The three Greek observers are stated to have inoculated two rabbits with lymph taken from a vaccine vesicle raised on a person suffering from "phthisis of the first degree." In one of the rabbits a tubercle was noticed at the point of inoculation at the end of twelve days, and after five weeks there was generalised tuberculosis. The author of these statements, in reply to my request for further particulars, expressed his regret that his notes were lost. Toussaint's experiments consisted in vaccinating a tuberculous cow on the vulva with lymph taken from a well-formed vaccine vesicle raised on a healthy child. On the seventh and eighth days—the pocks being then umbilicated—he took lymph and with it inoculated four rabbits, a pig, a cat, and a pigeon. Two of the rabbits were killed two months later, and were found to be suffering from tubercle at the point of inoculation, in the lungs, and in the lymphatic glands. The other two rabbits, killed just when they were going to die, were also tuberculous. The pig was killed 142 days after inoculation, and was found to be

[1] The original communication (14) was made in 1881: "Note présenté à l'Académie des Sciences le 8 Août, 1881. Infection tuberculeuse par les liquides des sécrétions et par la sérosité des pustules de vaccin."

suffering from widely-distributed calcareous and caseous tuberculous nodules. The cat and the pigeon were killed on the sixtieth day and did not shew any sign of tubercle.

These experiments are quoted because they are the only ones, so far as I am aware, which have been seriously advanced in support of the above statement made by Degive. They should be accepted with great reserve, as the sources of fallacy in their method are obvious. The first series, without more detail, which unfortunately cannot now be given, can hardly be said to have any demonstrative value; the second series (Toussaint's) are inconclusive, as the vaccination was performed on a part which, if any tuberculous excreta were passed, could hardly fail to be contaminated. It may be pointed out that the cow selected was obviously tuberculous, and that experiments performed with lymph taken from the cow on the seventh and eighth days, and from vaccine vesicles in such a position and in such circumstances, can have little or no practical bearing on the transmission of tuberculosis in the ordinary course of vaccination.[1] If any further evidence were needed to shew how little reliance can be placed on these experiments in support of the allegation that there is in fact a substantial danger of inoculating tuberculosis with vaccination, it may be pointed out—

1. That vaccine lymph is obtained from calves and not from adult cows; and even if it were obtained from adult animals, those obviously tuberculous would not be selected for the purpose.[2]

2. That calves are very little liable to tuberculosis. It is stated by Fürst (20), on the authority of Pfeiffer, that only one case of "perlsucht" occurred during the first four months of life amongst 34,400 calves; and these numbers are borne out by the statistics of the abattoirs at Augsburg and Munich, only one tuberculous calf being found amongst 22,230 at the former place, and even less frequently at the latter (29). Yet this almost inappreciable source of danger can be avoided by the simple precaution of not using the lymph from any calf until the animal has been killed and proved to be entirely free from disease. Such, indeed, is the practice in some parts of Germany.

Besides those mentioned above, a large number of experimental inquiries have been undertaken to ascertain whether the lymph taken from the vesicles of a person undoubtedly suffering from tuberculosis contains tubercle bacilli, or is capable of transmitting tuberculosis to susceptible animals. Amongst them may be mentioned those of Josserand, Acker, Lothar Meyer, Straus, and Peiper. Josserand's and Straus's papers contain references to inoculation experiments, and Peiper's article contains

[1] In the Minority Report of the R.C.V., paragraph 219, p. 202, it is stated that "the experiments of Toussaint indicate the possibility of inoculating tubercle upon animals by vaccination" (reference being made to answer 22,714). But no new facts are brought forward.

[2] The calves used for the L.G.B. supply of vaccine lymph are carefully examined, and if there be any suspicion of tuberculosis the whole of the lymph-pulp from that calf is destroyed. The "lymph" is also treated with glycerin which destroys tubercle bacilli.

references to a considerable number of cases of tubercle accidentally inoculated. None of these observers were able to detect tubercle bacilli in the lymph raised on tuberculous vaccinifers (human or bovine); and none of the animals inoculated with the lymph taken from Straus's cases shewed even a suspicion of tuberculosis after inoculation. In Josserand's cases the post-mortem examinations gave negative results in forty-three of the forty-seven animals inoculated; not one gave conclusive evidence of tuberculosis, and one only had enlargement of the glands in immediate relation to the point of inoculation. The lymph in these cases was obtained by vaccinating individuals obviously tuberculous; and, when thus obtained, it was used for inoculating the animals experimented on by injecting it into the peritoneal cavity, under the skin, or into the anterior chamber of the eye; so as to produce the maximum result. In fact the experiments were done in a manner which could not possibly have its counterpart in vaccination. Further, it is important to bear in mind that it is very difficult to obtain tuberculous infection by simple scratching of the skin; and this fact, which is in accordance with common experience, has received confirmation from Chauveau's (15, 9) experiments. He found that in five instances in which he endeavoured to produce tuberculosis by means of inoculation through the medium of the skin, not only were the results negative, but also no sign of tubercle was found in any of the scars. It is probable that in those cases of local tuberculous inoculation which occur after tattooing, cuts, and the like, the wound has always penetrated the skin so that the infection took place in the subcutaneous tissue. No undoubted case of invaccinated tubercle was brought before the Royal Commission on Vaccination; but Sir T. Barlow has reported one case in which lesions, believed to be tuberculous, appeared in the skin of a child who had been vaccinated three months previously. The vaccination in this case pursued a normal course, and there were no tuberculous lesions affecting the vaccination sites or the lymphatic glands in the axilla on the same side as the vaccination. The child's father had died of some acute pulmonary disease of three months' duration, probably tuberculous.

A similar case is recorded by Marocco (26, 20). In this instance the child died of tuberculosis four months after being vaccinated with calf-lymph. The pocks healed well, and subsequently disseminated red papules appeared; these suppurated, and caseous abscesses formed round the joints. No details are given of previous or family histories, so that this may have been no more than one of those coincidences which must occasionally occur after vaccination, without any causal relations between the operation and the subsequent event.[1]

[1] In the Minority Report R.C.V. 1895, paragraph 219, p. 202, it is stated that "it has been found that tuberculous disease can be readily conveyed from infected animals to healthy animals or persons by the medium of infected animal products such as milk." Although in certain circumstances this statement may be correct, it has little or no direct bearing on vaccination. Tubercle bacilli have never yet been detected in vaccine lymph, even when raised on tuberculous individuals (such as could not possibly be selected as vaccinifers).

I have seen only one case of death from acute miliary tuberculosis in an infant within the first few weeks after vaccination: in this case (No. 207, Appendix ix. to the Final Report of R.C.V., p. 397) the wounds healed completely, and about twelve weeks after vaccination the child died of acute miliary tuberculosis. The post-mortem examination shewed that there was no induration in or around the vaccination scars, which were well and firmly healed; nor was there any enlargement of the axillary or cervical glands. There was, in fact, nothing in the condition of the scars, or of the glands in relation with them, to suggest that the vaccination and the tuberculosis were in any way connected.

From the facts which up to the present time have been brought to light, it would seem to be certain that the communication of tuberculosis in the course of vaccination is of such exceeding rarity that it is even doubtful whether it has ever been so transmitted. This latter conclusion has been arrived at by many observers both on practical and scientific grounds. Bollinger goes so far as to say that the inoculation of tuberculosis in vaccination is to be denied absolutely; and Dr. Heron, who has paid great attention to the question of the transmissibility of tuberculosis from one individual to another, informs me that he does not know of any recorded case in which the transmission of tuberculosis or lupus could rightly be attributed to vaccination.

Vaccination and lupus.—Lupus affecting the seat of vaccination has been observed in some few instances; but it is much to be regretted that in none of the recorded cases with which I am acquainted has it been possible to determine with anything approaching to certainty whether the disease was invaccinated, or whether the case was merely an ordinary lupus attacking the vaccination scar; or even to shew whether the lymph came from a contaminated source, or was presumably capable of exciting any but the specific effects of vaccination. Mr. Hutchinson (21) and Vidal (10) are of opinion that, in the cases recorded, there is not sufficient ground for believing that lupus resulted directly from vaccination, but that it was due to the patient's constitutional tendencies. There is some justification for this opinion; but there is no evidence that lupus can be transferred by inoculation from one person to another. Vidal, indeed, states that his numerous attempts to accomplish it have failed.

Dr. Colcott Fox informs me that he has seen a case in which lupus began in one of the vaccination scars shortly after the sore had healed. Subperiosteal tuberculous nodules, with a disseminated lupus, afterwards appeared; and after death it was found that the child was suffering from pulmonary tuberculosis. There is no record in this case of the source of lymph; and, as one other child in the same family died of

And, further, the milk of tuberculous cows is only known to be infective when there is local tuberculous disease in the mammary gland. There is no evidence that the milk of tuberculous individuals in whom the gland is healthy either contains tubercle bacilli or is capable of communicating the disease. This opinion is shared by Dr. Sidney Martin, to whom I am indebted for information on the subject. It must also be remembered that Prof. Koch has expressed grave doubts as to the transmissibility of bovine tuberculosis to the human species through infected food.

tuberculosis, it is possible that this child was already tuberculous at the time of vaccination, and that the operation acted merely as the exciting cause of the acute disease: this often happens in children after the exanthems, and even after mechanical injuries. In the only case of post-vaccinal lupus which I have myself seen and investigated ((2) and cf. Sixth Report of R.C.V., p. 141), the evidence was very inconclusive. The child was vaccinated in four places, two of the vaccination wounds did not heal completely, and two are stated not to have healed for two years; the lupus from which the child afterwards suffered is believed to have originated in one of the scars; and when the case was first seen five years later, the whole of the vaccinated area was involved (see

FIG. 20.—Lupus affecting the seat of vaccination. Drawn 9 years after the operation. For details of the case see text, and Case 26, p. 242, Appendix ix. to Final Report R.C.V. 1896.

Fig. 20). This child was the second of six children, and no member of the family was known to be tuberculous. The source of the lymph could not be traced. Cases reported by Lennander and Besnier are not more conclusive. The one was seen eighteen years after vaccination; the other more than thirty-four years afterwards. In Lennander's case vaccination is said to have been normal; and though lupus had commenced in the scar, and there was a small ulcer when the boy was ten years old, a doctor was not consulted about it until he was seventeen. When first seen by Lennander, the appearances of the original sore had been much altered by treatment; but the case was proved, on microscopic examination, to be tuberculous. No conclusion seems to be warranted from these cases, except that lupus may attack a vaccination scar, as it may attack any cicatrix; and, even supposing the local lesion to have no causal relation with vaccination, it is remarkable, seeing

how frequently lupus occurs, that there are not more cases on record, similar to those given above, in which the disease attacked the scars.

Vaccination and "scrofula."—The further question arises whether vaccination be in any way responsible for the production of the chronic tuberculous diseases which are included under the names tabes mesenterica and scrofula. The number of children amongst the labouring classes who suffer from these complaints makes it certain that some infants will sicken and die of them within a few weeks or months of vaccination; and, although vaccination may be in no way the cause of the disease, it may and must always be difficult in such cases rightly to apportion the precise effect of inheritance, circumstances, and vaccination—especially if, owing to feeble health, degenerate tissues, and bad surroundings, vaccination has been followed by ulceration, glandular abscess, or some such complication likely to excite febrile disturbance. A long inquiry into such a case will be found on p. 374, App. to Final Report R.C.V. 1896. Further, the length of time necessary for the evolution of the disease is so protracted that the all-powerful factors of inheritance, circumstances, food, clothing, and so forth, which exert their influence on the lives of all infants, have full time to make themselves felt, and render it practically impossible to draw sound conclusions from individual cases. In order, then, that some estimate may be made as to the effect of vaccination on the prevalence of the diseases named, a wider survey must be taken. During the forty years ended 1896 the Registrar-General's returns shewed an increase in the number of deaths ascribed to tabes mesenterica and scrofula, and a decrease in the allied diseases of hydrocephalus and phthisis. How much of this was due to better diagnosis and to transference of cases from one class to another it is impossible to say; but that the increase is not due to vaccination may be inferred from the Leicester statistics, which prove to be a useful standard for comparison. In Leicester the increase in deaths from tabes mesenterica and scrofula during 1883-87, as compared with the years 1863-67, was 25·8 per cent; the increase for England and Wales during the same period was 26·8 per cent; from this it may be inferred that, within reasonable limits of error, Leicester is, in this respect, as badly off without vaccination as the rest of England is with it. In the opinion of those best qualified to judge, the facts brought before the Vaccination Commission do not warrant the assertion that the increased mortality from the diseases under consideration is in any way due to vaccination (18).

Vaccination and leprosy.—It has often been asserted that leprosy can be, and has been, spread by vaccination; and some few individual cases have been brought forward as evidence in favour of the view. To determine whether this is possible it must be shewn:—

1. That leprosy can be communicated directly by inoculation.
2. That leprosy bacilli can be detected in vaccine vesicles raised on a leper at the place where the skin is healthy.
3. That individual cases have been observed in which, from the

evidence, there is good ground for believing that leprosy has been accidentally invaccinated.

The evidence on the first point, namely, the general question of the communicability of leprosy directly from one individual to another, is conflicting and contradictory. A case recorded by Dr. Hawtrey Benson is important as giving ground for the suspicion that in exceptional circumstances the disease may be so communicated. In this instance, two brothers lived and slept together; one had contracted leprosy in the "Indies." He died, and three years later his brother, who had never been out of the United Kingdom but had worn his clothes, shewed symptoms of the disease. This case is far more convincing than those which occur in countries where leprosy is endemic; though it does not justify any deduction as to the reality of the alleged danger of communicating the disease by vaccination. So far as the evidence goes at present it must be considered extremely doubtful whether the disease has ever been communicated directly or indirectly in the ordinary course of this operation.[1] Notwithstanding all that has been said by those who are of opinion that the increase in leprosy, which has occurred in some of the places where the disease is endemic, is largely due to vaccination, not one case in which there was any sufficient evidence to justify such a statement was brought before the Royal Commission of 1889-96. On the contrary, those who have had the widest experience and the best opportunities of forming a correct judgment—such men as Dr. Hansen of Bergen, and the late Dr. Beavan Rake, medical superintendent of the Leper Asylum at Trinidad—did not consider that any such inference could be drawn from the data available. These opinions, weighty in themselves, are supported by the fact that in New Zealand, Iceland, Norway, and India, leprosy has steadily declined (19), although vaccination has been widely practised; while in the Sandwich Islands it has at the same time largely increased. Dr. Hansen has never seen a case of invaccinated leprosy; he informs me that in 1890 he sent out a circular to all physicians in Norway, asking whether they had observed any case of leprosy occasioned by vaccination. This inquiry failed to trace a single case in which there was ground for believing that leprosy had been so caused. The importance of such a statement is obvious when it is remembered that vaccination is efficiently carried on throughout the country.

To prove that there is prima facie ground for believing that leprosy may be invaccinated, reference has been frequently made to the following experiments made by Arning (3, 4). He inoculated the left forearm of a native Hawaiian with a portion of leprous nodule; a month later the man suffered from pain in the left shoulder, elbow, and wrist, with painful

[1] The whole question will be found fully discussed from the scientific point of view in the *Journal of the Leprosy Investigation Committee*, i. 5-11, 130, 141; iii. 90; iv. 32-41, 72, and from the opposite side, in the *Recrudescence of Leprosy and its Causation*, by W. Tebb, London, 1889. See also Beavan Rake, *Medical Record*, New York, 1893, vol. xliv. p. 705, and *Report on Leprosy for the year* 1892, Trinidad, 1893; also Phineas Abraham, *Trans. VII. Internat. Congr. of Hygiene*, London, 1892, vol. i. p. 384.

swelling of the ulnar and median nerves. During the next six months the neuritis gradually subsided, and a small leprous nodule formed at the point of inoculation. Leprosy bacilli were present for six months. Two and a half years later the symptoms of leprosy were definite; and a year afterwards the disease was at its height. The fallacy of drawing any deduction from such a case, to prove the danger of inoculating leprosy by vaccination, is too obvious to need comment; for, apart from the fact that vaccination does not consist in inoculation with leprous tissue or cultures of leprosy bacilli, the man came of a leprous family, and lived in a place where leprosy was endemic. Even Arning himself does not appear to consider that the case proves conclusively that leprosy was inoculated.

Inoculation experiments have been made by other competent observers, especially by Danielssen and Hansen; but the results were entirely negative.

Arning (5) detected leprosy bacilli in the lymph of vaccination-vesicles raised on the skin of an advanced case of tubercular leprosy; but he did not detect any in lymph from two cases of anæsthetic leprosy. On the other hand, Drs. Beavan Rake (7) and Buckmaster (24) examined a large number of cases in a similar manner, and in most cases did not find any trace of bacilli. In the cases in which the part vaccinated was obviously diseased they found suspicious-looking rod-like bodies; but, as Beavan Rake stated, even if the doubtful cases be admitted as evidence that leprosy bacilli are to be found in a vaccine vesicle raised on a patch of tubercular leprosy, it has no bearing on the question at issue; since no responsible person would think of vaccinating a leper on an affected part, and using lymph from vesicles so obtained for further vaccinations.

The conclusions these observers arrived at are as follows:—

1. That the alleged cases of transmission of leprosy by vaccination are open to serious doubt.

2. That, assuming the presence of leprosy bacilli to be necessary to produce leprosy, no danger need be apprehended from the vaccine lymph even of an actual leper; provided he be vaccinated on healthy skin.

Turning from the experimental to the practical side of the question the evidence is even less precise and conclusive. Two series of cases have been repeatedly quoted as giving some ground for the suspicion that leprosy might be communicated in the ordinary process of vaccination. The first of these cases was recorded by Sir W. T. Gairdner[1] and is as follows:—

Dr. X., living in a tropical island where leprosy was endemic, vaccinated his own son from a native child, and from his own boy in turn vaccinated a third child. Both the latter in after-years suffered from leprosy. The

[1] "A Remarkable Experience concerning Leprosy," etc., *British Medical Journal*, 1887, vol. i. p. 1269. I have made every effort to trace the vaccinifer in this case, as it is one not only of scientific but of practical interest. Dr. X. is dead: Mr. Racker, who wrote to Mr. Tebb (30) saying that he knew all about the case, gave the wrong initials for the father and the wrong name for the school at which the boy had been, so that his statement requires confirmation: neither Sir W. T. Gairdner, Dr. Buckmaster, Dr. Beavan Rake, nor Dr. W. Tebb knew more of the case than stated above. I have not received any reply to the inquiries I have addressed to Mr. Racker and Dr. Pasley, who both speak as though they were acquainted with the circumstances.

native child was said to have come of a leprous family, and Sir W. T. Gairdner writes that he "understood (though perhaps not definitely so stated) that leprosy had declared itself in the native child after vaccination"; of this fact, however, there was so much uncertainty that in a subsequent letter to the *British Medical Journal* (13) he modified this statement, and says that the doctor's child was vaccinated from a native child who was "probably not an actual or apparent leper." Thus, in this much-quoted case there is no evidence that the children, who some years later became lepers, were in fact vaccinated from a child suffering at the time from leprosy. Neither is it known that the latter subsequently became a leper. Again, there is no information as to the date or situation of the first appearance of the leprosy; and during the time which intervened between vaccination and the development of the disease the children appear to have been living in a country in which leprosy was endemic. So much attention would not be called to this case were it not that it has been almost invariably quoted as one in which the two boys who suffered from leprosy had been vaccinated from a native child who afterwards became leprous;[1] and much greater weight has been attached to it on this account than it rightly deserves.[2] The other classical cases are reported by Daubler (16). Two women were vaccinated from a patient who subsequently died of tubercular leprosy. In both instances leprous nodules first appeared on the forehead and cheeks; in the one case eighteen weeks, and in the other about eight weeks after vaccination. They were not seen by Daubler until some years later (probably about 3½); and there is no evidence to shew that the vaccinifer was leprous at the time when vaccination was performed: nor in either case was there any evidence that the disease began in the vaccination scars, or subsequently affected them. It is worthy of note that leprosy appeared in both cases in less than five months; and as the late Dr. Beavan Rake remarked, clinical experience does not warrant the belief that a disease so essentially chronic as leprosy is produced so soon after inoculation. Other similar examples might be given; but the above will suffice to shew that it is doubtful whether leprosy can be inoculated even in exceptional circumstances. Should this possibility, however, be proved, the disease could hardly be inoculated under the conditions which occur in vaccination; since, apart from the fact that a person suffering from leprosy or coming of a leprous family would not in any circumstances be used as a vaccinifer, there is ground for believing that vesicles developed on healthy skin do not contain the specific virus capable of communicating leprosy.

Vaccination and cancer.[3]—There is no authentic case on record in

[1] Cf. Beavan Rake and Buckmaster, *Journal of Leprosy Investigation Committee*, No. 4, p. 32; *Report of Leprosy Commission in India*, Appendix I. p. 414; Beavan Rake, *Medical Record*, New York, *loc. cit.* p. 708; Phineas Abraham, *loc. cit.* p. 6.

[2] Cf. C. F. Carter, *Leprosy and Vaccination in British Guiana; Journal of Leprosy Investigation Committee*, No. 4, p. 39; and Phineas Abraham, *loc. cit.* p. 3, note.

[3] Objection may be raised to the use of the word "cancer" as too vague. It is the term used by Mr. A. R. Wallace. Here it is not restricted to its technical meaning, but includes all forms of malignant neoplasm.

which cancer has resulted from vaccination; neither have I seen nor been able to trace any case of cancer affecting the vaccination scar. No mention would be made of the subject, were not cancer one of the diseases the increase of which has been attributed to vaccination (32).

Apart from this clinical evidence, which is very strong, the statistical evidence is still stronger; as may be seen from the following facts:—

1. The mortality from cancer during each quinquennial period of the first fifteen years of life has decreased.[1]

2. The increased mortality from cancer is greatest at the period of life furthest removed from vaccination.

3. The whole of the recorded increase in cancer has taken place in inaccessible cancer; that is, in circumstances in which exact diagnosis is difficult.

4. There has been practically no increase of cancer in accessible parts.

The whole subject was ably worked out by Mr. George King, late actuary of the London Life Office, and Dr. Arthur Newsholme (28), who, after examining all the evidence, drew the conclusion that the increase in cancer is apparent only, and is due to improvement in diagnosis and more careful certification of the causes of death.

Vaccination and epizootic disease.—No case of epizootic disease resulting from vaccination, or associated with it, has, so far as I am aware, been recorded in this country. Three cases of aphthous stomatitis occurring during the vaccination period, and in many ways resembling epizootic stomatitis (foot-and-mouth disease), came under the observation of L. Voigt of Hamburg; but inasmuch as many similar cases occurred in the neighbourhood, and there was also an outbreak of the affection amongst the cattle, there does not seem to be any ground for supposing that its occurrence in the vaccinated children was anything more than a coincidence: of the three children mentioned one had temporary discomfort, a second died of cholera at the same time as its father, and one only was seriously ill with the symptoms in question. This child, in whom the attack began on the tenth day after vaccination, suffered severely with high fever, stomatitis affecting the lips, tongue, and gums. A dusky papular eruption, which subsequently caused much irritation, appeared first on the lips, cheeks, and genitals; later it spread over the whole body, and ended in a severe folliculitis: this was complicated by bronchopneumonia. The child eventually recovered, vaccination having pursued a normal course (*vide* also p. 692).

[1] Final Report R.C.V. par 391, p. 102.

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CONCLUSION [1]

General considerations.—The foregoing pages have shewn that the danger from vaccination, as carried out in the United Kingdom, is in individual cases very small; from invaccinated disease it is almost nil: and although in a fractional percentage of cases grave complications arise, in almost every instance they are due to inflammatory or septic affections such as are common to all wounds, and are found to depend far more on various extraneous circumstances than on any properties inherent in the lymph itself. Serious results, the direct consequence of constitutional affections such as generalised vaccinia, or of cutaneous eruptions such as impetigo or eczema, will probably continue to occur in some few cases from causes which cannot at present be foreseen; but, as has been shewn, they are exceptional and their number small.

Children after vaccination are at all times liable to suffer from various harmless rashes of an erythematous or urticarial type, which, though for the most part free from danger, not infrequently give rise to considerable distress. Children are peculiarly liable to such eruptions from any cause which produces local irritation or disturbance of the digestive system. It is unlikely that any precautions in the selection of lymph would

[1] This section is largely founded on a memorandum prepared by Sir T. Barlow and myself for the Royal Commission on Vaccination, 1896; and reference is frequently made to the recommendations of the Commission, *q.v.* Final Report R.C.V. pp. 113-116.

materially lessen the number of such cases; but it is essential that those who have the care of vaccinated children should be scrupulously exact after the operation in avoiding all extraneous sources of irritation to the wounds, more especially in those children who are known to be liable to eczema or other eruptions. If the instructions to public vaccinators under contract issued by the Local Government Board (1898) are carried out in the spirit as well as in the letter,—if the child be healthy, its circumstances wholesome, the lymph carefully prepared and properly used, and if reasonable care be exercised after vaccination,—there is no doubt that the dangers of the operation are infinitesimally small (cf. note, p. 698).

The various sources of risk, and the safeguards which they suggest, may be considered under the following headings:—The child and its circumstances; the treatment of the arm; the lymph, and methods of preparation; the vaccinator, and methods of vaccination.

The child.—*Age.*—Although there is good ground for believing that under favourable conditions vaccination may be carried out successfully on infants of a few days old, the custom in some infirmaries and lying-in institutions of vaccinating children shortly after birth is not infrequently productive of dangerous complications; and the practice [1] is to be discouraged except at times when there is danger from small-pox: in this case the infant should, if possible, be kept under observation until the arm is healed.

There are two obvious sources of danger in vaccinating very young infants.

i. A considerable number of the children born in our workhouses, infirmaries, and lying-in charities are born in circumstances which entail distress and disgrace on the mother; consequently they are often feeble, and sometimes diseased.

ii. The mother may take her discharge and leave the institution just at the time when the child's arm is most inflamed; thus she may return to conditions of life which cannot fail to be harmful to the child.

If, from the prevalence of small-pox, it be necessary to vaccinate newly-born children, it might in these exceptional cases be advisable to vaccinate in two or three places only, on account of the tender age of the child. The certificate of successful vaccination, however, should be withheld, and any parent, whose infant was thus vaccinated, might be required to have it vaccinated fully at the expiration of a year from the first operation.

Previous Health of Child.—In many cases which I have inquired into, the child, previous to its vaccination, had been suffering from some ailment which could not fail to affect its general health. Among these may be mentioned convulsions, diarrhœa and vomiting, tuberculous glands, eczema, and so forth. Again in several cases the child had just been weaned, or put on some new kind of food, or fed unsuitably or insufficiently. The vaccination of such children is contrary to the regulations issued by the Local Government Board, which require that care should be exercised in

[1] Final Report R.C.V. p. 115, par. 441.

the selection of children for vaccination; and that the operation should not be performed, as it sometimes is, on children who are obviously unfit. Now that the time-limit for vaccination has been extended to six months it will give vaccinators more freedom in this selection, and enable them to defer the operation when the child's health is uncertain.

Circumstances.[1]—There is risk (*a*) in vaccinating children in houses in which there are cases of acute infectious disease: (*b*) in bringing them at the time of vaccination into direct or indirect contact with infectious disease: (*c*) in exposing them to possible infection from sloughing or open wounds, purulent ophthalmia, or discharges of any kind: (*d*) in subjecting them after vaccination to unhealthy conditions, such as result from gross sanitary defects. Cases of vaccinal injury resulting presumably from each of these causes have been investigated and recorded. No open wound would be expected to pursue a normal course under such conditions; but persons responsible for the care of children among the poor often, from ignorance or negligence, disregard the most ordinary precautions.

It is desirable that simple instructions on these essential points should be given to every person who has a child vaccinated; and the form of such instructions should not be left, as it is at present, to the individual vaccinator. Some public vaccinators give careful instructions, as a matter of routine; but the practice is not general.

Attention should be called to the fact that whereas inquiries were made for the Commission into cases of alleged vaccinal injuries in all parts of England, not a single case amongst the well-to-do classes came under the notice of Sir T. Barlow or myself. With few exceptions the cases of injury which we investigated occurred amongst the poor and ill-fed, living under conditions so insanitary that it was well-nigh impossible that the children could be healthy. In this class the lives of infants are exposed to far greater dangers than in the well-to-do classes; and even a trivial operation such as vaccination must be attended with a certain amount of risk, the risk being dependent far more on the condition of the child than on the nature and normal effects of the operation.

Treatment of the arm.—*Treatment of Insertions.*—Risk is often incurred by parents who, in the desire to lessen the severity of vaccination, wipe the lymph off the arm without due regard to the manner in which this is done; dirty fingers or dirty pocket-handkerchiefs are used, and the result often is irritation of the parts, excessive inflammation, glandular abscess, or some septic complication.

Treatment of Vesicles.—One of the most frequent causes of vaccinal injury is the ignorance of the parents, and their disregard of the most elementary rules of cleanliness. Considering the variety of decomposable substances which are sometimes applied to the vaccination vesicles in a manner well calculated to accelerate decomposition, it is remarkable that the harm done is not greater than it is (cf. Vaccinal Ulceration, p. 707). It cannot be doubted that so long as ignorance prevails as to the

[1] Final Report R.C.V. p. 115, par. 445.

importance of cleanliness and the avoidance of mechanical irritation of the wounds cases of injury will occur from time to time. The only way to combat these dangers is to instruct the parents in the care and treatment of the child and of the vaccinated arm before and after operation.

Shields.—In many cases severe inflammation has been caused, or certainly aggravated, by the use of shields. The shield is apt to rub the scabs off the vesicles and to produce an open sore. This danger is further aggravated when these shields are foul with pus from old vaccination wounds, as they not infrequently are kept and used for one child after another without being cleansed. In all cases the use of shields should be discouraged.

Dirty Sleeves.—A similar source of danger is that of allowing a pus-soaked sleeve to rub into and irritate the vaccinal wounds. Ulceration and suppuration frequently arise from this easily removable cause.

Opening of Vesicles.—As has been pointed out, the majority of cases of erysipelas occur *after* the first week. It would seem to be desirable that the opening of the vesicles should, as far as possible, be avoided.

The lymph and method of storing.—*The lymph.*—In a small proportion of cases the lymph has been found primarily and directly responsible for vaccinal injury. In these cases the fault generally lies in the application or use of the lymph. Certain very exceptional cases have, however, occurred in which, although as far as could be ascertained the lymph was normal, some abnormal result—such as generalised vaccinia—has followed its use.

Sources and Preparation.—It has not been possible to determine with any precision the relative frequency with which complications have followed the use of calf or of humanised lymph, or the use of lymph stored on points, in tubes, or as a conserve. Abnormal results occasionally follow the use of each of them; but as there has been no possibility of determining the total number of vaccinations performed in each way, there are no data for ascertaining the relative results of the several methods respectively.

The general impression left upon me by my inquiries is that vaccination *direct from the calf* tends to produce more severe inflammatory reaction than that which has been glycerinated, and that calf-lymph treated with glycerin or chloroform is free from most of the objections which have been urged against humanised or crude calf-lymph. But it should not be forgotten that as yet there is nothing to prevent private practitioners from using humanised lymph, or lymph imported from abroad without any guarantee (except the maker's reputation) as to its origin. Whilst at the same time the glycerinated calf-lymph prepared under skilled supervision in the government laboratories is issued only to public vaccinators, in spite of the recommendation of the R.C.V., *loc. cit.* p. 113, par. 437, which is as follows:—"So long as the State, with a view to the public interest, compels the vaccination of children, so long even as it employs public money in promoting and encouraging the practice, we think it is under an obligation to provide that the means of obtaining

calf-lymph for the purpose of vaccination should be within the reach of all. We have no hesitation, therefore, in recommending that steps should be taken to secure this result. Whether the duty of providing calf-lymph should be undertaken by the Local Government Boards in the several parts of the United Kingdom, or whether some other method would be more advantageous, can be better determined by those who have had practical acquaintance with the working of the vaccination laws."

The storage of lymph, treated with glycerin, in tubes [1] (as now practised by the National Vaccine Establishment)—each tube containing only sufficient lymph for one vaccination—is probably the method least open to objection. It is of practical importance that only sufficient lymph for one vaccination should be contained in each tube, as serious results have been known to occur from the use of a tube of lymph which had been opened for a previous vaccination.

Vaccination and the vaccinator.—*Methods of Vaccination.*—Cases of severe inflammation, abscess, erysipelas, and septic infection have followed the use of some mechanical vaccinator, or of the Cooper Rose needle. Such mechanical contrivances to shorten the process of vaccination would with adequate sterilisation do no harm, and might serve a useful purpose; but they do not and hardly can receive the vigilant attention which is required to keep them surgically clean. Their use should, therefore, be strongly condemned; and attention should be called to the fact that it is essential that instruments used in vaccination should be as carefully sterilised as for any other operation. Nothing but an ordinary lancet or needle is required, and the instrument should be much more thoroughly sterilised than is frequently the case; this can best be done by immersion in some antiseptic or in boiling water, and by wiping each time, after use, on a fresh piece of sterilised wool. Such elementary precautions as these are not always observed by those who vaccinate, although they are insisted on in the Local Government Board's instructions to public vaccinators.

Postponement of Vaccination.—In all cases in which vaccination has been postponed it is desirable that a certificate, stating the causes of postponement, should be produced at the time when the child is subsequently vaccinated; so that the risk of taking lymph from the vesicles of a child known to be unhealthy may be rigidly excluded.

Position of Pocks.—Ulceration not infrequently results from placing the insertions so near together that the vitality of the tissues between them is destroyed, and a slough is produced. This risk may almost certainly be obviated by following the Local Government Board's instructions, and leaving at least half an inch between the pocks.

Repeated Vaccination.—In a few cases there is ground for believing that harm has resulted from revaccinating a child a week after a first vaccination has proved unsuccessful. It appears to be desirable that vaccination should not be repeated until at least four weeks have elapsed since the date of the first insertion.

[1] Cf. evidence before the R. C. on Vaccination by Dr. Copeman, and in *Journ. Path. and Bacteriol.* Edin. and London, 1894, vol. ii. p. 407.

Certificates of Vaccination.—There seems to be a certain amount of hardship involved in the fact that in the case of a private patient a certificate of successful vaccination may be, and sometimes is, given for a result which would not be accepted, and rightly so, by a public vaccinator. Instances occur in which a certificate of successful vaccination has been given by a private practitioner for one insertion; whereas four insertions would be made by the public vaccinator. It is obvious from this that a certificate of successful vaccination has no definite meaning, and does not necessarily shew that a child has been properly vaccinated. It is desirable that every certificate of vaccination should specify the number of successful insertions.

District Nursing in regard to Vaccination.—It is part of the duty of a public vaccinator to attend to a child in case of any serious consequences of vaccination. But in populous districts, and in places where the services of a trained nurse are available, great benefit might result from having a competent person to act under the direction of the vaccinator, and to visit at regular intervals such cases as at the first inspection might be found abnormal. Many cases of the inflammatory kind might be quickly relieved by boracic lint, fomentations, or simple antiseptic methods properly applied. Moreover, a trained nurse might render material service in instructing the poor in due cleanliness, and in the avoidance of injury to the arm in dealing with their vaccinated children; she could also give timely warning of the danger of sanitary defects or of exposure to infection from the specific fevers. Many accidental complications might thus be avoided.

Summary.—To secure successful vaccination, cleanliness, in the surgical sense, the careful selection of lymph from healthy children whose antecedents are known if humanised lymph be used, or the examination of the calf after death if calf-lymph be used, and the postponement of vaccination in the case of all feeble, cachectic children, or of those suffering from cutaneous eruptions, are essential. If these simple precautions be honestly carried out, the risk of invaccinated disease, or of any complication resulting directly from vaccination, will in the great majority of cases be obviated.

Since, with few exceptions, the complications which arise are not peculiar to vaccination, it is unnecessary to speak at length about their treatment. The most important points are to keep the pocks dry and clean, and to preserve them from mechanical injury. They may be dusted with starch and iodoform powder, or with gallate of bismuth, or protected with an antiseptic covering. If ulceration should occur it may be necessary to use some stimulating lotion, such as solution of chloride of zinc (grs. 10 to 40 to the ounce), or solution of hypochlorite of soda; but as a rule careful washing with warm water, or with a solution of boracic acid (grs. 20 to the ounce), will suffice without any more powerful application.

The treatment of such complications as erysipelas, glandular abscess, eczema, impetigo, does not call for special comment. There is nothing in them peculiar to vaccination, and they may be treated without reference

to the foregoing operation, provided only that the pocks themselves be kept free from injury, and in a healthy state. Lastly, it is above all things necessary that the child's general health should be attended to, and that it should not be vaccinated immediately after weaning, or after any other important change has been made in the method of feeding. There is a general disposition to regard vaccination as so trivial an operation that no precautions are necessary to ensure the well-being of the child, and to forget that the local pock is but the expression of a constitutional disturbance which is effecting a change in the whole being of the individual under operation.

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LIST OF SPECIAL WORKS OF REFERENCE

The following works will be found to contain a great number of references to the literature of vaccination, in addition to those already given :—

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T. D. A.

PATHOLOGY OF VACCINIA

By S. M. COPEMAN, M.D., F.R.S.

PRACTICE OF VACCINATION

What is vaccinia ?—It is, in the human subject, a specific communicable disorder characterised by the appearance of a local eruption passing

through the stages of papule, vesicle, and pustule, associated with more or less constitutional disturbance.

These symptoms are produced, indifferently, by the inoculation of lymph derived from vesicles similarly brought about in a previous case in the human being or the calf, or from the eruptive vesicles of a disease of milch cattle called cow-pox. Such inoculation process, whichever way induced, is known as vaccination. This name was originally devised by Dunning, inspired doubtless by the terminology of Jenner, who wrote of the disorder under the title of Variolæ vaccinæ. In this manner Jenner gave expression to his belief that the malady commonly known as cow-pox was in reality nothing more or less than small-pox of the cow.

But soon it was discovered that if there were such a malady as "small-pox of the cow," there was also a small-pox of the horse, which, under the name of "grease," was resorted to as a source of vaccine lymph. Loy was the first to distinguish, in any satisfactory fashion, constitutional grease from a merely local affection; and thus he explained the failure of many experimenters to transmit horse-pox to the cow.

That a constitutional disease of the horse characterised by a vesicular eruption can be induced by the inoculation of this animal with the virus of cow-pox or vaccinia, has been shewn experimentally by Chauveau, who injected vaccine lymph subcutaneously, and also into the lymphatics and blood-vessels of colts. In nearly half the number of cases operated on the injection of the lymph was followed by a generalised eruption which Chauveau called "horse-pox." In all probability Jenner was mistaken in his assumption that "grease," in the sense of horse-pox, was a necessary antecedent to cow-pox; but at the same time there can be little doubt that these two diseases are very closely allied, if indeed they be not identical.

That this is so is shewn by the fact that numerous strains of vaccine lymph have, from time to time, been raised from the equine source—the protective power of which against small-pox we have reason to believe was equal to that of lymph of undoubted bovine origin. As, however, it is obvious that cow-pox was the source of the lymph-stocks first introduced into use by Jenner and his contemporaries, it will be of interest to study briefly the nature and clinical appearances of this disease as seen in the cow and also in man; whether accidentally contracted or intentionally inoculated.

Cow-pox in the cow.—For a description of cow-pox in its typical form, as it was known to Jenner and his contemporaries, it is necessary to consult the writings of the early part of the last century, at which period the attention of the medical and scientific world had been specially directed to this affection of cows by the teaching of the apostle of vaccination. Probably the most trustworthy accounts are those published by Bryce of Edinburgh, and later by Ceely; and it is from their statements that the following description of the malady is derived.

According to these observers this affection, when once set agoing in a herd, tends to spread with considerable rapidity, the "matter" of the vesicles being carried by the hands of the milkers from one cow to

another. It makes its appearance especially in the spring season, and is observed upon the udders and teats of the cows; at first in the form of small vesicles containing a limpid fluid. These vesicles are of a bluish or livid colour, and may be surrounded with considerable erysipelatoid swelling and inflammation. If ruptured the vesicles tend to become irregular about the edges; and, unless care be then taken, are very apt to degenerate into foul and troublesome sores. During the course of the affection the cow is not infrequently observed to be in bad health; the appetite is impaired, the temperature is above normal, and the secretion of milk may be considerably diminished. If the material from the vesicles on the udders or teats of the cows happen to come in contact with an abrasion of the skin of the milker's hand, such person is apt to become infected with the disease. When the ailment is communicated in this manner it is termed *casual cow-pox* to distinguish it from the less virulent form which is intentionally propagated by inoculation. Probably the more severe form in which casual cow-pox usually appears is to some extent due to the situation of the resulting vesicles, and to the purulent nature of the secretion from the sores on the cows' teats or udders.

Casual cow-pox in man.—When cow-pox has been communicated to the milkers in the casual way, small inflamed spots appear in a few days upon the hands, more particularly about the joints and tips of the fingers. These spots quickly assume the appearance of small blisters, somewhat resembling those from burns, and go on increasing until they become large vesicles of a circular form, with a flat or rather a concave surface; their edges being considerably elevated above their centre. They have then acquired a somewhat bluish colour and are found to contain a limpid fluid. After some days the parts around the base of these vesicles become considerably swollen, hard, and inflamed; and, as the affection advances, they may assume a somewhat erysipelatous appearance. Pain and some degree of swelling of the axillary glands now denote an absorption by way of the lymphatics, and, with the usual symptoms of fever, mark a constitutional affection which is sometimes so severe as to incapacitate the person from following his usual employment for some days. It does not appear, however, that a general eruption ever follows even on the smartest attack of casual cow-pox. After a few days the pain, inflammation, and hardness of the surrounding parts gradually abate; but the vesicles not infrequently ulcerate instead of becoming encrusted and drying up. These ulcerations, however, gradually heal up in course of time without occasioning any lasting injury; and the constitutional affection, although severe, is usually transient and unattended with danger: there is no case on record in which casual cow-pox has proved fatal.

Inoculated cow-pox (Vaccination) in man.—In the cow-pox induced by inoculation the appearances which present themselves may differ, in some respects, from those which have been described as occurring in the casual disease. Thus, about the third day after the insertion of the virus of cow-pox, either by puncture or by slight incision in the arm, a small

inflamed spot may be observed at the point where the inoculation was performed. Next day this spot appears still more florid ; and, on passing the point of the finger over it, a certain degree of hardness and swelling is readily perceptible. By the fifth day a small pale vesicle occupies the spot where the inflammation began ; and the affection begins to assume the characteristic appearance of cow-pox. The vesicle has now a milky-white colour without any inflammatory zone around it, it is evidently depressed in the centre, and its edges are considerably elevated. For the next two days the vesicle increases in size and retains the same character, so that by the seventh day it may have acquired very considerable magnitude ; if the inoculation be performed by a puncture, it assumes a circular form ; if done by an incision, an oblong form. But in both cases the margin is regular and well-defined ; while, the centre becoming still more depressed and the edges becoming more turgid, the whole puts on an appearance which is very characteristic of this particular affection. About the eighth day from the time of inoculation an inflammatory zone begins to appear around the base of the vesicle. This increases for two or perhaps three days more, by which time it may be two inches or wider in diameter and of a bright red colour. At this period, also, the vesicle still retains its concave appearance ; a central crust has commenced to form and begins to assume a dark or brownish colour. About the eleventh day the vesicle has attained its greatest magnitude, and the surrounding inflammation begins to abate. The fluid in the vesicle, which before was thin and transparent, is now more viscid and slightly turbid. After this period the whole becomes quickly converted into a smooth, shining, and somewhat translucent dry crust of a dark brownish or red colour. This crust, unless forcibly removed, will adhere for a week or more and then fall off, leaving the skin beneath apparently sound, but livid for a time, and more or less permanently scarred.

In children little else than the above local process is usually noticeable ; but in adults constitutional symptoms are apt to be somewhat more severe. About the eighth day from the time of inoculation the glands in the axilla may become a little swollen, and usually there is some pain and stiffness on moving the arm. Headache, shivering, a rapid pulse, and other febrile symptoms occasionally present themselves ; and these may persist for a period varying from a few hours to two or more days.

The relationship of variola and vaccinia.—Almost from Jenner's day the value of the practice of vaccination has been impugned by some on the plea that inoculation of one disease—"cow-pox"—could not be expected to exert any really protective action against the disease of small-pox, supposed to be totally different. And, if the thesis of essential difference between these maladies were capable of demonstration, no doubt the objection would be of considerable weight. For there exists little well-authenticated evidence, if any, that the living virus of one disease is capable, when inoculated into an animal, of affording protection against the effects of inoculation of the virus of another and totally different disease ; although, no doubt, when two different viruses

are inoculated at nearly one and the same time the incubation-period of the second infection may be somewhat prolonged.

During the long period which has now elapsed since the introduction of vaccination, many observers have attempted, by experimental methods, to solve the problem of the true relationship of variola to vaccinia. These attempts have, for the most part, been directed to the possibility of giving rise to cow-pox by the introduction, in one or another manner, of the matter of small-pox into the system of the bovine animal. In the great majority of such attempts, which are vastly more numerous than is generally supposed, the results have been altogether negative. Such was generally the case, not only in the experiments of Sonderland, Ceely, Chauveau, and others, who endeavoured to introduce the contagion through absorption by the respiratory or circulatory organs, but also in the still greater number of attempts to bring about infection of the system by means of inoculation on the skin. In certain instances, however, these inoculation experiments have been attended by results which as shewn in the Report of the Royal Commission on Vaccination fall into one or other of three categories :—

The first category includes the experiments in which the inoculation of small-pox matter into the udder, or adjoining parts, of the bovine animal gave rise, at or near the seat of inoculation, to a vesicle, either identical in visible characters with the ordinary vaccine vesicle produced by inoculation with the matter of cow-pox, or to a vesicle the features of which, while not corresponding wholly with those of a perfect vaccine vesicle, so closely resembled it as to justify the recognition of the vesicle as a vaccine vesicle. Also it includes experiments in which, though the local result had not the characters of a perfect vaccine vesicle, yet lymph from it, when carried through a second or third remove in the cow or calf, presented results fully manifesting those characters; and when again transferred to man gave results undistinguishable from the ordinary vaccine vesicle. Indeed, lymph of such a pedigree has come into general use for vaccination purposes. Of these experiments, the best known and most quoted are those of Thiele (1838), Ceely (1840), Badcock (between 1840 and 1860), Voigt (1881), Haccius and Eternod (1890), King (1891), Simpson (1892), and Hime (1892); but there are several other experimenters. The details of the experiments are very scanty in the cases of Thiele and Badcock; but more full in the others, especially perhaps in those of Ceely and Haccius.

In *the second category* may be placed the experiments of Drs. Klein and Copeman. Dr. Klein, who in 1879 had obtained in thirty-one trials what then appeared mere negative results, found in a renewed research in 1892 that the result of the first inoculation in the calf of small-pox matter was not a distinct vesicle, but merely a thickening and redness of the wound. Lymph pressed from the thickened wound, when inoculated into a second calf, produced a like but rather more marked result; while the thickening and reddening still further increased as the process was repeated in a third and in a fourth calf. Lymph squeezed from the

wounds of a fourth calf produced in a child typical vaccinia, and crusts from the child produced in turn typical vaccinia in a calf. The writer, in his earlier experiments, obtained somewhat similar results; the appearances increased in three removes and approached those of typical vaccinia, but did not reach them.

The third category consists of the results obtained in an elaborate inquiry conducted by a Commission of the Society of Medical Sciences at Lyons, with Chauveau at its head. These results, reported in 1865, were briefly as follows:—Inoculation of the cow or heifer with small-pox matter in any one of the thirty animals used did not give rise to a vaccine vesicle: nevertheless a definite result was obtained, in the form, however, not of a vesicle, but of a thickening and inflammation of the wound; when a puncture had been made this became a papule: lymph squeezed from such a papule, and inserted into a second animal, gave rise to a like papule; and this again might be used for a third animal, but often failed; and the effect could in no case be carried on through more than three or four removes. When the inoculation was repeated on an animal on which a previous inoculation had produced such a papule, no distinct papule was formed; and, moreover, lymph squeezed from the seat of the latter inoculation produced no effect at all when used for the subsequent inoculation of another animal. There is evidence that the development of the papule was the result of the specific action of the virus. This inference is strengthened by the fact that no such papule was produced by the Lyons Commission when the small-pox matter was inserted into an animal which had previously had cow-pox naturally or artificially; as well as by the fact that when an attempt was made to vaccinate, with vaccine lymph of proved efficacy, an animal on which a papule had been so developed by inoculation with small-pox matter, the vaccination failed; though the animal had never had natural cow-pox nor been vaccinated.

The specific nature of the lymph of the "Lyons" papule is held to be shewn by the fact that such lymph, when used on the human subject, gave rise to small-pox. On the other hand, it has been urged that in this case the virus producing the effect was simply the original small-pox matter used in the inoculation, producing the papule and still clinging to the wound. This, however, is considered to be disproved by the experience that lymph from a "Lyons" papule of the second remove also gave rise in the human subject to small-pox. Thus, Chauveau and his Commission found that small-pox implanted in the bovine animal gave rise to a specific effect which was not cow-pox, but was of the nature of small-pox; though its manifestations in the cow were different from those of small-pox in man.

With the exception, then, of Chauveau and his colleagues of the Lyons Commission, all the observers mentioned claim to have obtained positive results—in a certain number of their experiments, at any rate—as regards the production of typical vaccinia, after one or more removes, as the result of variolation of the calf.

By no one, prior to the writer's more recent experiments, had success

been constantly attained; and it is among the experiments of the earlier observers especially, who made use, for the most part, of heifers and milch cows, that the largest proportion of abortive attempts are to be met with. Subsequent experience has shewn that success is much more likely to be attained if calves be used instead of heifers or cows. In this way, perhaps, Chauveau's somewhat anomalous results may be in part explained.

In seeking an explanation of the difficulty so frequently encountered in experimental attempts to transmit human small-pox to the bovine races, attention may profitably be directed to the fact, not perhaps sufficiently realised, that a great deal, at any rate, of the small-pox which was prevalent at the time that Jenner lived and wrote, was of that comparatively mild variety which, under the name of inoculated small-pox, was intentionally produced in healthy subjects, with the object of thereby conferring protection against subsequent attack by the disease in a virulent form. So mild, indeed, at times, were the results of inoculations in the hands of such operators as Adams and the brothers Sutton that, as we learn from contemporary records, in many instances but little obvious effect was observed, with the exception of the local vesicle arising at the site of insertion of the small-pox virus, and the patients suffered but little inconvenience. Thus, more particularly in certain of Adams' cases, as may be gathered from his own account of the circumstances, the visible effect produced so closely resembled the results then beginning to be known as following on the Jennerian process of vaccination, that numbers of his patients were with difficulty persuaded that he had not, contrary to their desire, intentionally vaccinated rather than variolated them. The gradual evolution of a strain of lymph of such tenuity, according to Adams himself, was obtained by attention to the mode of life and general treatment of persons undergoing the process, together with careful selection of the "source" (preferably the "primary vesicle") from which the virus was obtained. The majority of persons thus inoculated are not likely to have been incapacitated, as the result of the operation, to a much greater extent than are those who undergo efficient vaccination at the present day, and, doubtless, therefore, they would be, for the most part, capable of following their ordinary avocations during the process of the induced disorder. On the other hand, this would have hardly been possible in the case of persons contracting small-pox in the ordinary way, among whom the disease was apt to exhibit such virulence as to account for the death of perhaps 50 per cent of those attacked.

Not only were the effects following on inoculation comparatively mild, but the disease, in this form, was intentionally brought into many country districts which otherwise might not have become invaded by small-pox. In the light of these facts, it occurred to the writer that it was not improbably from the *inoculated* form of small-pox, rather than from the ordinary variety of the malady, that much, at any rate, of the cow-pox, in the pre-vaccination era was derived. It is not difficult to understand

how the cracks so often found on the udders of cows might become infected by a milker with fingers contaminated by contact with the inoculation sore upon his arm. The writer determined, therefore, to put the matter to the test, and in default of inoculated small-pox in the human subject, the necessary material was experimentally obtained from the monkey, an animal which is readily susceptible to the inoculated disease. The results of this investigation may be briefly summarised as follows:—

In each of four separate series of experiments the human small-pox lymph or pulp was first inoculated directly on calves, and, in every instance, so far as could be observed, with altogether negative results. But with monkeys, success was as invariably obtained, and when, after one or more passages through this animal, the contents of the local inoculation-vesicles were employed for insertion on the calf, an effect was now produced which, after two or three removes in that animal, was indistinguishable from typical vaccinia. Moreover, from the contents of vesicles raised in this manner on the calf, a number of children have, in turn, been vaccinated, some of whom were afterwards kept under observation for as long a period as a couple of months. Every such vaccination "took" normally, and in no case was any bad result subsequently observed; no "generalisation" of the eruption occurring in any instance.

Since then it can be conclusively proved that small-pox lymph, by passing through the system of the calf, with or without the monkey as intermediary, can be so altered in character as to become deprived of its power of causing a generalised eruption, while inducing at the site of inoculation a vesicle undistinguishable from a typical vaccine vesicle; and more important still, since it can be shewn that when transferred again to man, it has by such treatment completely lost its former power to produce a general disease, it may fairly be asserted that cow-pox—or rather, that artificially inoculated form of the disease which we term vaccinia—is nothing more nor less than variola modified by transmission through the bovine animal. Perhaps the most reasonable interpretation of such results may be that small-pox and vaccinia are both of them descended from a common stock—from an ancestor, for instance, which resembled vaccinia far more than it resembled small-pox. It is conceivable, indeed, that the seeming vaccinia, obtained in the calf by inoculation of small-pox matter into that animal, may after all be but a reversion to an antecedent type; and in this connexion we may call to mind a fact of universal experience, namely, that vaccinia, however it may have arisen in the past, or is made to appear in the present, exhibits little tendency to "sport" (as, for instance, by manifesting a "generalised eruption") in the direction of small-pox.

Mr. Picton and Dr. (now Sir W.) Collins, in their addendum to the *Report of the Royal Commission on Vaccination*, lay much stress on the want of "evidence to shew that inoculation of the pox of the cow on the human skin has ever produced small-pox." Variola and vaccinia may,

nevertheless, have a common ancestry, since it is not unlikely that variola may have departed widely from the original type, and have gained an exalted virulence by successive reproduction in man under conditions favourable to its propagation and activity. If this evolution of the disease has, in fact, taken place, variola may have suddenly reverted, under greatly changed conditions, to an ancestral type. But the reverse process is not to be expected. It is most unlikely that a less differentiated form, also emanating from the common ancestral stock, should attain to the most exalted virulence in a single individual, and *per saltum* declare itself as small-pox, as the dissentient Commissioners insisted that it ought to do.

Bacteriology of vaccinia and variola.—We owe the first step towards the elucidation of the micro-pathology of vaccinia to Chauveau and to Burdon-Sanderson, who by means of filtration and deposit experiments demonstrated, almost concurrently, that vaccine lymph, when freed from its contained particles and inoculated on a living animal, no longer causes vaccinia; while, on the other hand, the precipitate or deposit when employed in similar fashion remains capable of producing the disease.

In consequence, numerous bacteriologists have since devoted themselves to the search in vaccine lymph for a micro-organism to which the special and peculiar effect resulting on the inoculation of such lymph is due. Owing, however, to the immense amount of work on the subject which has been published even within recent years, it would be unprofitable here to attempt to set out any detailed account of such work. But it may be stated that the evolution and development of the vesicle is liable to be accompanied by the appearance of vast numbers of bacteria, of one and another kind, the ancestors of which were probably, to some extent at any rate, introduced beneath the surface of the skin at the time of performance of the vaccination, since the purer the lymph and the greater the antiseptic precautions observed in connexion with the operation, the less, as a rule, will be the number of bacteria in the resulting vesicle. The results of all the more recent investigations on the bacterial flora of calf-vaccine clearly demonstrate the fact that calf-lymph (or rather vesicle-pulp) usually contains a large number of micro-organisms which are in no way concerned with its specific activity, and to which, for this reason, the writer originally applied the term "extraneous." Those species which are most commonly met with are, morphologically and culturally, identical with the staphylococci found in pus, viz. the *Staphylococcus pyogenes aureus*, *albus*, and *cereus flavus*. Occasionally the streptococcus of pus may be present, as also the *Staphylococcus citreus*. It should be stated, however, that the fact that in vaccine lymph micro-organisms are found which, in certain circumstances, are known to be provocative of suppuration does not in any way imply that the lymph in which they occur is purulent, or that, if such staphylococcus-infected lymph were employed for vaccination of the human subject, suppuration would necessarily ensue. Other microbes of a purely saprophytic nature that are met with include the

common hay bacillus, *Bacillus mesentericus*, varieties of proteus, yeasts, moulds, and sarcinæ. These, however, can for the most part be excluded by careful manipulation, so that, in vesicle-pulp which has been collected with all due precautions, nothing is usually found beyond some one or more of the four mentioned first staphylococci, of which a white staphylococcus is perhaps most common, and possibly one or more yeasts.

In 1894 the writer, concurrently with Dr. Klein, recorded the observation that, in specially stained specimens of vaccine and variolous lymph, taken at a period antecedent to full maturity of the vesicles, the presence of bacilli of extremely small size and in practically pure culture can be demonstrated. These bacilli cannot be found, or only with difficulty, in mature lymph, for the reason, probably, that they have by then given rise to spores. For some time it appeared impossible to obtain further evidence as to the rôle of these bacilli, as they altogether refused to grow on any of the ordinary culture media, and under either aerobic or anaerobic conditions, though this very fact tends to shew that they are not of a merely saprophytic nature. On the other hand, the fact that these apparently identical bacilli are to be found both in vaccine and in variolous lymph of about the fifth day of eruption, tends to support the hypothesis that they constitute the active contagium of the diseases in question. Although not capable of growth on gelatin, agar, serum, and so forth, cultures of these small bacilli were eventually obtained, in some few out of a large number of experiments, by inoculation into hens' eggs, which were subsequently incubated at a temperature of 37° C. for periods ranging from a fortnight to a month. And as recorded elsewhere, in certain instances calves inoculated with the contents of these eggs exhibited by the third remove a vesicular eruption, the lymph obtained from which was successfully employed for the vaccination of a large number of children.

Psorosperms or sporozoa in lymph.—In consequence, no doubt, of the apparent impossibility of isolating from vaccine lymph any bacterium which could be regarded as peculiar to vaccinia, several observers have sought to prove that organisms of a somewhat higher order than bacteria might be concerned in the production of this malady, and also of variola. For instance, bodies believed to be of the nature of "psorosperms" or sporozoa have been described in and among the epithelial cells of an inoculated area by Pfeiffer, Guarnieri, Monti, van der Loeff, Doehle, and Sicherer on the Continent; by Dr. Ruffer and Mr. Jackson Clarke in this country; and, more recently, by Councilman, Calkin, and their collaborateurs in America. Dr. Ruffer and Mr. Plimmer described the alleged parasite as a small round body which sometimes appears to have a more darkly staining centre. It is, they say, about four times the size of an ordinary staphylococcus, and generally lies in a clear vacuole in the protoplasm of the epithelial cells of the stratum Malpighii, and occasionally indents the nucleus, though it has not been found enclosed in the latter body. These observers state that they have found the same organisms in sections of

skin from small-pox patients and in small-pox pustules of the larynx and trachea. Pfeiffer describes similar bodies, not only in the epithelial cells of the vaccine vesicle, but likewise in all other vesicular eruptions of man and the lower animals. Pfeiffer, Guarnieri, Ruffer and Plimmer all assert that these parasites exhibit very slow amœboid movements. (For a description of Cytoryctes see Professor Minchin's article on "Protozoa" in the volume on Tropical Diseases and Animal Parasites.)

There can be no doubt, of course, as to the occurrence of the appearances described, although we may not be prepared to accept the interpretation put upon them; and in this connexion it is well to bear in mind that the bodies enclosed in cells described by Guarnieri, Monti, and Ruffer are said by them to differ essentially in their staining reaction and in their appearance from those of Pfeiffer, van der Loeff, and others. It may be added also that no such bodies have been satisfactorily demonstrated in vaccine lymph itself. It is therefore not improbable that the "parasites" in question represent merely the result of a specific irritation of the epithelial cells of the skin, consequent on the inoculation of vaccine lymph containing the living virus of the disease.

A Small-pox Antitoxin.—Inspired by the investigations of Tizzoni and Cattani on tetanus, and, later, of Behring on diphtheria, attention has been directed for some time past to the production, if possible, of an antitoxic serum, which might be of use in the treatment of small-pox, for when once this disease is fully manifested vaccination is practically of no avail. The results of experiments in this direction recorded by different observers are, however, somewhat conflicting.

Thus Kramer and Boyce were unable to produce any immunity even with large doses of serum from vaccinated calves; and Beumer and Peiper arrived at a similar conclusion. On the other hand, Kinyoun, and Hlava and Houl claim successful results; but, so far as can be judged from their publications, such claim would appear to rest on somewhat slender foundation; although Hlava and Houl state that in one instance the injection of their serum to the extent of 0·6 to 1·0 c.c. per kilo of body-weight of the experimental calf entirely prevented the action of vaccine lymph inoculated four days later. They have not as yet put on record any experiment with variola.

The fullest and most recent contribution to this subject is that of Béclère, Chambon, and Ménard. The conclusion at which these authors arrive is that the serum of a vaccinated heifer, gathered after the drying of the pustules, immunises to a certain extent against the effects of subsequent vaccination; but the diagrams with which the paper is illustrated shew that the antagonism is by no means complete.

History of various lymph-stocks.—Jenner's first case of vaccination was that of a boy, eight years of age, whom he inoculated on the arm with cow-pox matter taken from a sore on the hand of a dairymaid who in turn had become infected with the disease from milking cows suffering from cow-pox. This was in 1796; but it was apparently not until two years later, in 1798, that he made his first attempt to carry on a strain

of lymph from arm to arm. In the spring of that year he inoculated a child with matter taken directly from the nipple of a cow; and from the resulting vesicle on the arm of this child first operated on, he inoculated, or, as it may now be more correctly termed, "vaccinated" another. From this child several others were vaccinated; from one of these a fourth remove was carried out successfully, and finally a fifth. Four of the children were subsequently inoculated with small-pox—the "variolous test"—without result.

At this point, however, the strain appears to have been allowed to die out; but, in January 1799, Woodville, one of the physicians to the Small-pox Hospital in London, who had been much interested in Jenner's investigations, discovered the presence of cow-pox in a dairy in Gray's Inn Lane. With lymph obtained from one of the cows in this dairy he vaccinated seven persons at the Small-pox Hospital; while in the case of certain other persons he employed matter from sores on the hand of a dairymaid who had become infected from one of the cows at this same place. These cases, from which afterwards in succession many hundreds of persons were vaccinated, were the source of what is usually spoken of as "Woodville's lymph." These strains were extensively distributed both by Woodville and also by Pearson, one of the Physicians to St. George's Hospital; but even at this period lymph from several other sources had also come into use. Thus Pearson very early obtained lymph from a dairy in the Marylebone Road and elsewhere; while Jenner, who, having for a time no supply of his own, had used some of Woodville's hospital lymph, obtained a further supply from a cow at a Mr. Clarke's farm in Kentish Town.

The lymph first employed on the Continent and in other foreign countries was undoubtedly supplied in large measure by Pearson and Woodville; although we learn from Baron and other authors that Jenner, who was naturally much appealed to for supplies of lymph, himself sent lymph to Stromeyer of Hanover, to De Carro of Vienna, to Berlin, and to Newfoundland. Strains derived from lymph-stocks, originally supplied by Jenner, were also sent abroad by various persons; the original strain being, in large measure at any rate, the lymph obtained by Jenner from the Clarke's Farm cow. It would be erroneous to suppose, however, that all the lymph employed abroad in the early days of vaccination was obtained from England. Indeed both Sacco and De Carro made extensive use of lymph obtained by the former from a case of natural cow-pox which he discovered in Lombardy. From this stock also De Carro sent supplies to Constantinople, where it was employed for the first vaccination carried out in that part of Europe. De Carro it was also who first succeeded in conveying a supply of lymph to India. This lymph, again, was not from Jenner's stock, but was of Milanese origin, having been furnished to him by Sacco. It was, moreover, not of bovine, but of equine origin, and, according to De Carro, had never been passed through the cow.

Among more recent strains may be mentioned that obtained in 1836 at Passy, in the environs of Paris, from the hand of a milker who had

contracted casual cow-pox. The old stock then in use at the Académie de Médecine had evidently degenerated somewhat; and, when its effects were compared with those of the new Passy lymph, the vesicles developed from the latter were found to be manifestly finer.

In 1836 Estlin of Bristol put in circulation a stock which at first shewed unusual activity. This abated, however, after some transmissions, and the lymph afterwards came into extensive use.

From this time onwards the various stocks became so numerous that Ceely, writing in 1841, states that during the preceding three years he had experimented with lymph from more than fifteen distinct sources; of these six had been taken from the natural disease, either direct from cows or from vesicles on the hands of the milkers, and seven were artificially produced in the cow.

A lymph-stock in use for a number of years at the Government Animal Vaccine Establishment was originally obtained on 26th November 1881 at a farm in the village of Lafôret, not far from Bordeaux; whence a sample of lymph from the seventeenth calf in succession from the animal first affected was sent by Dr. Dubréuilh, of Bordeaux, to the Medical Officer of the Local Government Board.

Of late years, more particularly, numerous strains of so-called variola-vaccine lymph, obtained by inoculation of human small-pox on the calf, have been introduced especially by Fischer, by Haccius, and by King, and have been transmitted through many thousands of individuals.

In discussing the origin of the various lymph strains at that time in use Dr. (now Sir W.) Collins and Mr. Picton, in their addendum to the *Report of the Royal Commission on Vaccination*, make a point of the impossibility, as they say, of employing the "variolous test" as a proof of the efficacy or the reverse of any particular lymph-stock. It is, indeed, a penal offence at the present time to inoculate a human being with variola, but to demonstrate that it is, nevertheless, by no means impossible to test the potency of any given sample of lymph by this method, mention may be made of certain experiments carried out by myself with the object of determining this question. Monkeys were employed, on account of their similarity in many respects to man; and it was found on experimental investigation that they are susceptible both to vaccinia and variola.

In the cases of variola and of vaccinia alike, the local result of inoculation attains its acme (*qua* vesiculation) in the monkey, as in the human being, about the eighth day. The first signs of reaction appear usually on the third day, by which time, if variolous lymph has been used, there is a distinct though very thin crust over the site of inoculation. The chief difference noted between the effects resulting from the local inoculation of these two diseases in the monkey is, that in the case of variola there is more or less of a crust from the first, that vesiculation is less marked than in vaccination, that about the ninth to the eleventh day a general eruption may appear, which, in some instances, covers the whole surface of the body, and that the final scab at the site of inoculation is not so elevated in the variolated as in the vaccinated animal. Proof having

been thus obtained that this animal is capable of being infected with both vaccinia and variola, and that it passes through these diseases in forms similar to those witnessed in man, it was determined to make trial of the protection against small-pox afforded in the monkey by previous vaccination, and of the protection against vaccination afforded by variolation; and it appeared desirable also to compare the effect produced by the use of human and of calf vaccine respectively. For this purpose humanised lymph was obtained from Birmingham, where it is stated that the same strain of lymph has been continuously carried on by means of arm-to-arm vaccination for upwards of thirty years; the calf-lymph was obtained from the Government Animal Vaccination Station in Lamb's Conduit Street, and small-pox lymph was supplied from the hospital ships in the Thames, from Warrington, and from Manchester. As the result of many experiments extending over a period of several months, it became obvious that the mutually protective power of lymph obtained from these three different sources when inoculated on the monkey is practically identical in all respects, the second inoculation having invariably been productive only of a negative result.

The criticism of Dr. (now Sir W.) Collins and Mr. Picton, therefore, falls to the ground; since if it be desired to apply the "variolous test" to any given lymph-stock, all that is necessary is to vaccinate a monkey with a sample of the lymph in question, and subsequently to inoculate the animal with potent small-pox lymph after the lapse of such period from the first operation as may be thought proper.

Morphology and chemistry of vaccine lymph.—Fresh vaccine lymph, taken before full maturity of the vesicle, is a clear, transparent, limpid fluid, almost colourless in man and slightly straw-coloured when obtained from the calf; this difference in colour depends on the varying quality of the normal pigment present in the blood-plasma. Calf-vaccine lymph is also somewhat more viscid than human lymph, and does not flow so readily when the vesicle is punctured; thus it is usually necessary to use compression forceps in the collection of calf-lymph. Examined microscopically, vaccine lymph contains a certain amount of epithelial débris, a few cells and portions of cells being always visible. Leucocytes are usually present also, the number depending on the stage at which the lymph is taken; few or even none are to be found in the contents of the vesicle when first formed, but at or after the period of maturation they may be so numerous as to render the lymph turbid, or even puriform. A few red blood-corpuscles may be noticeable, although most observers will hardly agree with the statement made by Dr. Husband to the Royal Commission on Vaccination that this is invariably the case.

In stained specimens, particularly, micro-organisms of one or more varieties can readily be demonstrated; the actual numbers being dependent to a certain extent on the care with which the lymph has been collected. The nature and significance of the various microbes which at one time or another have been isolated from specimens of vaccine lymph has been discussed in the section on Bacteriology (p. 754).

It is matter of common knowledge that untreated lymph, when stored in capillary tubes, is apt after a longer or shorter interval to become cloudy, in which circumstances it is also liable to be uncertain in its action when subsequently used for the operation of vaccination. This opaque appearance may be quite independent of any coagulation of the lymph, as may not infrequently be demonstrated on breaking tubes in which it is most marked. On the other hand, where clotting has taken place after the lymph has been stored, the opacity tends to form with the coagulum a central whitish thread in the midst of a clear fluid, instead of being distributed through the lymph in discrete points as may otherwise be the case. If cultivation experiments be carried out by inoculation on nutrient media, the number of colonies resulting from such inoculation with the contents of tubes which have become opaque is usually much greater than if fresh lymph be employed in a similar manner. We are apparently justified, therefore, in considering that the opacity of old stored lymph is, in the main, the outcome of an enormous multiplication of aerobic bacteria, the ancestors of which are present in the lymph when first collected; although their numbers are then so comparatively small as not to render it in any way turbid. It follows that vaccine lymph which has become opaque should never be employed for vaccination.

Vaccination lymph, chemically speaking, consists of the serum, or rather of the plasma of the blood. When freshly obtained, therefore, it is faintly alkaline in reaction; but it becomes distinctly acid after a time when stored. In addition to the various salts and proteids normally present in the blood-plasma, vaccine lymph contains some substance, possibly of the nature of a toxin, which results from the vital activity of the specific organism peculiar to vaccinia. That this is so may be proved either by filtration of the lymph through porcelain or by exposure of it to a temperature of about 50° C. If such filtered or sterilised lymph be inoculated on the skin in the usual manner, no obvious effect is produced at the point of inoculation; but it will be found that the animal has been rendered temporarily immune to the effects of subsequent vaccination with lymph of normal potency.

Histology of the Vaccine Vesicle.—During the evolution of the local changes which result from the insertion of vaccine lymph beneath the surface of the skin, it is possible, as previously indicated, to recognise three more or less definite stages of papule, vesicle, and pustule. The same statement holds good with reference to the eruption of small-pox, whether this be local, *i.e.* due to intentional inoculation of the virus on the skin, or general, as the result of casual infection, with the exception that the edge of the vesicle resulting from inoculation is apt to be less regular in outline than is that of the vaccine vesicle.

In each instance the appearance of the first or *papular* stage is brought about by inflammatory reaction, causing an increase of intercellular fluid, together with concomitant increase in volume and number of epithelial cells, of the rete Malpighii more particularly. The papule

gradually becomes enlarged by a circumferential extension of the same process, and owing to further changes in the cells first affected, vacuoles arise in the central portion of the papule, by the extension of which this ultimately becomes a vesicle.

The *vesicle* is a multilocular structure, the dissepiments, by means of which its interior is divided up, being formed from the thinned and extended remains of the original epithelial cells. Owing to the fact that the process of vacuolation increases, for a time, more extensively at the advancing edge of the vesicle, the central portion remains somewhat less elevated, thus giving rise to the appearance termed "umbilication."

At a somewhat early stage of the process an outflow of leucocytes takes place towards the point of injury. In time, each blood-vessel becomes the centre of an aggregation of leucocytes, which, by the rapid increase in their numbers, eventually transform the originally clear inflammatory exudation into a more or less purulent fluid. The vesicle is said now to have become converted into a *pustule*.

By the thinning and ultimate rupture of its trabeculæ the pustule finally becomes unilocular. The turbid fluid contained in it now gradually dries up, and, together with the necrosed remains of epidermal cells, takes part in the formation of the *crust*, which, under the microscope, appears as a homogeneous mass which takes an intense coloration when treated with the ordinary laboratory stains.

Meanwhile a regeneration goes on underneath the crust, the new epidermis being formed by an ingrowth from the surrounding *stratum lucidum*. The extent to which the *cutis vera* has been involved determines the depth of the resulting scar.

Practice of Vaccination

Collection and storage of vaccine lymph.—Previous to the year 1899 the use of arm-to-arm human lymph had been insisted on in this country in the case of all vaccinations performed at public stations, for the reason that until recently this was the only method by which lymph-stocks could be perpetuated, and the greatest possible purity of the lymph ensured.

In view, however, of the recommendations of the Royal Commission, embodied in the Vaccination Act of 1898, this method has been discontinued, so far as public vaccinations are concerned, in favour of the use of calf-lymph, with the object, among others, of diminishing the very remote possibility of the conveyance of syphilitic infection by the operation of vaccination (p. 712). By this change of method the Commissioners also considered that the necessity for opening vaccination vesicles, and thereby of affording opportunity for other local infections, would be avoided—such precaution being in their opinion a desirable one, although they added that its importance has been exaggerated.

If human lymph be required, the vesicle should be opened by a number

of minute punctures, which must be made on its surface and not around its base. The object of such multiple punctures is to open the various cell-spaces in which the lymph is contained; that of puncturing on the surface rather than around the base is to avoid any admixture with blood. Lymph soon collects in droplets at the points of incision, and may be removed on a lancet; or, if required for use at a distance, may be taken up into capillary tubes. On no account should the vesicle be pressed or squeezed in order to increase the flow of lymph, supposing the amount to be but scanty; and, on the other hand, if it be very thin, and consequently flow too readily, it should not be employed for use in vaccination.

The collection of calf-lymph is a matter of rather more difficulty, as, owing to its greater degree of viscidity and to the closer texture of the cell-spaces in the vesicle, it does not flow readily when the vesicle is punctured. For this reason it is necessary to employ compression forceps, between the blades of which the vesicle is taken up and confined by means of a catch while the lymph is being removed.

Lymph, whether human or calf, that is not required for immediate use may be preserved either in a dry state on "points"; or in the liquid condition, in capillary tubes which must be hermetically sealed after being filled.

The points used for the dry storage of lymph have hitherto been made of ivory, but it has been suggested that celloidin would be a more suitable substance for the purpose, as a smooth non-absorbent surface would be thus obtainable. They are usually about a couple of inches in length, and pointed at one end.

In order to charge the points they, in this country, are well dipped in the lymph exuding from a vesicle; and when a fair-sized drop has been collected on them, they are placed on some raised and flat surface, such as a plate turned upside down, with their moistened ends over the edge, until the lymph has thoroughly dried.

They should be kept until needed in a clean, well-stoppered bottle. To prepare the lymph for use, a small drop of water is placed on the end of the "point" in order to moisten the dried material. This may now be removed with the point of the vaccinating lancet, or the end of the "point" may be rubbed over scarifications of the skin previously made with a lancet. In the *Report of the Royal Commission on Vaccination*, however, the opinion is expressed that safety would be increased by preserving the lymph in tubes instead of on "dry points."

The capillary tubes employed for the purpose of lymph-storage should be similar to those first introduced by Dr. Husband of Edinburgh. In order to fulfil their intended purpose they should be (i.) large enough to contain sufficient lymph for one vaccination; (ii.) long enough to admit of both ends being sealed hermetically without subjecting the charge to the heat of the flame; (iii.) of such tenuity that they can be sealed instantaneously in the flame of a spirit lamp; and (iv.) of such strength as not to break easily in handling. To fill a capillary tube it should be

held in a more or less horizontal position, and one end applied to the drop of lymph exuding from a vesicle which has been punctured, when the lymph immediately enters by capillary attraction. No more should be allowed to enter than is sufficient to fill the tube from one-half to two-thirds of its length. The tube is sealed by applying the empty end to the flame of a candle or spirit-lamp, as much as possible of the contained air having been previously driven out by momentarily plunging into the flame the whole of that portion of the tube in which there is no lymph. By this means, as soon as the extremity is sealed, the column of lymph is driven by atmospheric pressure towards the end first closed; and the point at which the lymph found entrance can then be sealed in the flame in the same manner as was the other.

Glycerinated Lymph.—The practically universal occurrence of extraneous microbes in vaccine lymph and the chance of addition, during or after vaccination, of pathogenetic organisms by the agency of careless people, whether vaccinators or persons having charge of infants, has been advanced as reasons for avoiding vaccination, on the grounds of the possible harmfulness of the extraneous organisms liable to be introduced into the lymph at the time of the operation or subsequently in the course of the evolution of the resulting pock.

This argument, however—so far as the microbes usually intimately associated with lymph are concerned—loses whatever weight it may have had, since I have shewn that by thoroughly incorporating four parts of a sterilised 50 per cent solution in water of chemically pure glycerin with one part of the lymph or vesicle-pulp, and afterwards storing the mixture for some weeks prior to use at a low temperature and protected from light, all the ordinary saprophytes found associated with lymph are eventually destroyed. This result is proved by the fact that no growth arises in any of the ordinary culture media inoculated with such glycerinated lymph. This statement applies equally to the bacillus of tubercle and to the streptococcus of erysipelas when they have been added experimentally to vaccine lymph.

In glycerinated calf-lymph properly produced we have then a preparation which, while even more efficient as vaccine than the original lymph, can be produced entirely free from the "extraneous" organisms which, at one time or another, have been isolated from fresh or stored lymph; with the possible exception, in the case of lymph obtained from the calf, of the spore-bearing *B. subtilis*—the common hay bacillus—which, however, possesses no pathogenetic properties. This statement, since the first publication in 1891 of the experiments on which it is based, has received ample corroboration from many other observers, among whom may be mentioned Chambon, Ménard, and Straus; Leoni, Kinyoun, and Klein.

There can be no doubt, therefore, of the superiority of this method of lymph-storage over the perhaps simpler methods which were previously employed in England. In Germany, Belgium, and elsewhere, for some considerable time past, and for various reasons, admixture with glycerin

has been made use of in the preparation and storage of vaccine material; but originally without knowledge of the peculiar action exerted by such treatment in the purification of lymph. Kitasato, for instance, published a series of experiments in which he sought to free vaccine lymph from extraneous bacteria by the addition of carbolic acid to the extent of 0·5 to 8·66 per cent. He states that in each case the carbolic acid was added to samples of trade lymph which had, however, already been diluted, in the process of preparation, with a mixture of glycerin and water.

In the preparation of glycerinated lymph on a large scale the calf, which on the previous day should have been injected with tuberculin in order to ensure that it is not suffering from tuberculosis, is strapped down to a table of special construction, and the abdomen is shaved from the pubes to the umbilicus: occasionally, when a larger surface is required, the inside of the thighs is also shaved. The shaved area is then thoroughly cleansed with soap and hot water, and swabbed with a solution of corrosive sublimate; and this in its turn is washed off with sterilised water. With a somewhat blunt scalpel superficial incisions are then made fairly close together over the whole surface of the shaved portion of the skin, care being taken to remove with a sterilised towel or blotting-paper any traces of blood which may appear. A sufficient quantity of glycerinated lymph must be now thoroughly rubbed over the incisions with the flat portion of the blade of the scalpel; and when this has dried in the calf may be removed from the table and returned to its stall. After the lapse of about ninety-six hours from the first operation, the calf is again placed on the table, and the epithelium and underlying vesicular pulp are removed by means of a steel spoon, firm pressure being employed so as to avoid as far as possible the presence of blood. The scrapings are collected in a Petri dish, or other suitable receptacle, and immediately weighed. To this material is then added four times its weight of a sterilised mixture of 50 per cent of chemically pure glycerin in distilled water; and the whole is thoroughly ground down together. The latter process is carried out either by hand, a small pestle and mortar being employed for the purpose, or, more rapidly and perhaps more efficiently, by means of a mechanical mixing machine.

The resulting mixture, or emulsion as it is sometimes called, which will be sufficient in amount for at least 2000 vaccinations, may be kept in bulk until required for distribution; it must be stored in a cool place and protected from the light. If desirable, however, it may be drawn up at once into capillary tubes, which should be of somewhat larger diameter than those which are commonly employed for the storage of unmixed lymph. If this be done the tubes should be filled about two-thirds full, and the ends then carefully sealed in the flame of a spirit-lamp or Bunsen burner. Dr. A. B. Green, working at the Government Laboratories, discovered that by passing chloroform vapour through vaccine emulsion the process of purification is much hastened, thus rendering it possible to cope with sudden demands for large quantities of vaccine lymph such as are likely to occur at times of small-pox prevalence.

But on the other hand, it would appear that the time during which such chloroformed emulsion may be expected to retain its full activity is usually less than when glycerin alone has been employed.

Insertion of vaccine lymph.—This process may be carried out either by puncture, by multiple superficial incisions, or by scarification. Doubtless the individual operator will attain the greatest measure of success by employing the method with which he is most familiar; but there can be little doubt that the method of insertion by scarification is the one which is most generally satisfactory. This statement applies not only to the use of fresh lymph, but also to stored lymph, whether on dry points or in tubes; and more particularly if the lymph has been preserved with glycerin.

The mode of operation is briefly as follows:—The arm should, if possible, first be washed with warm soap and water, and afterwards carefully dried with a soft towel, gentle friction being employed so as to cause a certain amount of distension of the cutaneous capillaries. Drops of lymph, corresponding in number to that of the vesicles which it is required to produce, are then to be placed on the surface of the arm, and the skin put slightly on the stretch with the fingers of the left hand. Next the skin is scarified by a method of cross-hatching, through the drops of lymph, by means of whatsoever instrument may be preferred, care being taken not to place the insertions too close together, lest the vitality of the tissues between them be injured.

An ordinary bleeding-lancet, the point of which has been slightly blunted, or a flat-headed surgical needle, are both very efficient for the purpose of scarification; complicated instruments should be avoided since, as a rule, it is difficult to keep them thoroughly clean (cf. also p. 744).

The special advantage of a needle is that a new one can be employed on every occasion; if a lancet or like instrument be employed, it is essential that it should be boiled or otherwise sterilised immediately before use; and, further, that it should be dipped into boiling water and wiped on a piece of sterilised cotton-wool, not only between each operation, but, in the case of arm-to-arm vaccination, in the event of the vaccinator having to return to the vaccinifer for the purpose of obtaining more lymph.

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VACCINATION AS A BRANCH OF PREVENTIVE MEDICINE

By John C. M'Vail, M.D.

The evidence of the power of vaccination over small-pox is probably as great as, if not greater than, can be adduced in support of any proposition outside the domain of the exact sciences. Indeed, when all the variabilities of the human body which is the subject of protection, and the possible variations in the power and activity of the protecting agency, are taken into account, the proof of the value of vaccination, both in volume and in completeness, is very remarkable. One of its most striking features is the convergence of differing lines of evidence towards the same conclusion. From whatever starting-place the subject be approached, the point reached is the same. In whatever manner the facts be questioned and cross-questioned, their reply is unequivocal and unvarying. If an investigator begin his inquiry with any alternative hypothesis in view, he soon finds that it will not meet the case. The first line of evidence naturally relates to

The Prevalence of Small-pox before and since the adoption of Vaccination

The question of *the antiquity of small-pox* has attracted many medical historians, among whom, perhaps, the most notable have been Holwell, Willan, Freind, and James Moore. The origin of the disease is hidden in the mists of antiquity. The appearances which in ancient Greece and Rome distinguished one epidemic disease from another are seldom stated, and there seems no good proof that small-pox was known or differentiated. But Holwell adduces evidence that in Hindustan and China it was known long before the Christian era. Willan points out that Eusebius (who was born about 267 A.D., and was Bishop of Cæsarea) describes a Syrian epidemic in 302 A.D. in such a way as to indicate strongly that the disease must have been variola. The account given in 581 A.D. by Gregory of Tours, of an epidemic there, leaves little doubt that what he described was small-pox; and the term "variola" was used by Marius, Bishop of Avenche, so early as 570 A.D. In Ireland the monastic records indicate that small-pox prevailed as early as 675 A.D., and frequently afterwards; the native names being Bolgagh and Galar Breac. In England during the dark ages there were no statistics, but small-pox was so much feared that charms and amulets were worn to keep it off; and the leech book of the Saxon

physician Bald, who flourished in the tenth century, contained six prescriptions for pock disease. He told how a "pock in the eye" was to be treated. In this century also, Razes, hospital physician at Bagdad, wrote his famous work, and it is noteworthy that pricking of the pustules as part of the treatment is recommended by both Razes and Bald, though the instrument in the hand of the English leech is not a needle of gold or silver but a humble thorn with which "to delve away each one of them." Razes quotes from writers in previous centuries—Ahron in the seventh and Messue in the ninth—and gives no indication of the disease being then regarded as of recent origin. In England, under the Normans, Gilbert Anglicus, about the time of Edward I., and John of Gaddesden early in the fourteenth century, wrote of small-pox, and fairly closely followed the Arabian writers. Coming to later centuries, though in this country exact statistics are still wanting, there is abundant evidence of the ravages of small-pox. The disease, indeed, finds a place in general literature, as well as in old vocabularies, and in two or three books dealing, after the fashion of the time, with health and sickness—Shakespeare, Fletcher, Ben Jonson and Donne mention it. Later still, Sydenham's writings on small-pox are well known, and his introduction and advocacy of a "cool regimen" in the disease is one of the foundations of his deservedly great reputation. Very curiously, however, though contemporary and earlier writers had unhesitatingly regarded the disease as infectious, Sydenham, probably influenced by his conception of epidemic constitutions of the atmosphere, does not describe small-pox as communicable from one person to another.

The extent to which small-pox prevailed is sufficiently indicated by the opinions which were held of its inevitability. Razes incidentally mentions that "hardly any one escapes" attack. His Greek translator, about the end of the tenth century, says that "every man is born liable" to small-pox. In the sixteenth century Mercurialis states that almost every person must have it once, and Vidus Vidius regards it as a disease attacking all persons in the course of their lives.

There is a curious record regarding small-pox in the village of Ware in Hertfordshire. In 1722 the population was 2515 and at the end of a small-pox epidemic in that year there were only 302 persons who had never had the disease. These 302 persons are not described merely as not having suffered from small-pox, but as "to have the small-pox." In Chester, according to Dr. Haygarth, in 1775 only 1060 persons out of a total population of nearly 15,000 had not suffered from small-pox at some time in their lives. At Kilmarnock in 1728-64, of every 1000 children born alive 161 died from small-pox. In Glasgow in the years 1783 to 1800 inclusive there were 5959 deaths from small-pox in a total of 31,088 deaths from all causes. In Warrington in 1773 there was a small-pox epidemic which caused 211 deaths in a total of 443 from all causes in a population estimated at fully 8000 (*Phil. Trans.* 1774). In Manchester, according to Percival, in the six years 1769-74, there were 589 deaths from small-pox, and

in 1773 the population of Manchester, exclusive of Salford, was 22,481, so that the mortality per million was 4359. For Liverpool, Haygarth gives the population in 1773 as 34,407, and says "the annual average deaths by the small-pox in Liverpool are 220," this giving a rate of 6394 per million of population. In Sweden in the years 1774 to 1800 inclusive the deaths from all causes were 1,524,602, and of these there were 119,073 from small-pox, the annual rate being 2049 per million of population. In Berlin in 1758-74 the deaths from all causes were 81,133, and from small-pox 6705, or nearly one-twelfth, and in 1783 to 1800 the total deaths were 98,643, and the small-pox deaths 7668, or one-thirteenth. Sir John Simon in his classical papers on vaccination has collected much interesting historical matter to which students of the subject may refer.

Small-pox Inoculation.—With regard to the prevalence of the disease in the eighteenth century, the influence of the practice of small-pox inoculation, or variolation, has been much discussed. But our knowledge does not justify a definite conclusion whether the good it did in protecting the inoculated was greater than the evil which it did in spreading the disease. On whatever side the balance for the eighteenth century should be struck, it is obvious that, quite independently of inoculation, small-pox in that century and in many previous centuries was one of the most fatal scourges of mankind.

Small-pox Prevalences since the Introduction of Vaccination.—It is necessary now to contrast prevaccination statistics of small-pox with those of more recent times. For this purpose the Royal Commission began by giving facts for the first quarter of the nineteenth century. The period selected, though somewhat remote from the present day, is excellent for the purpose in question. It immediately followed the introduction of vaccination. The adoption of the practice was of course far from universal, but it is to be remembered that at the beginning of the nineteenth century a very large proportion of the population had already suffered from small-pox in the ordinary way, or had been protected by variolation, so that only a minority of the people required protection. The unprotected percentage it is impossible to estimate, but, looking to the previous prevalence of natural and artificial small-pox, it cannot, I think, have amounted to anything like one-half of the population, probably not even to one-quarter. It was among this minority that vaccination was practised, and the extent of the practice must have greatly reduced the percentage of the population who had been subjected to neither variola nor vaccinia.

Another feature of the period 1800-1825, though not referred to in the Royal Commission's Report, is yet most important. For many years after the beginning of the nineteenth century the great bulk of the vaccinations could be regarded as recent, and the need for revaccination had hardly arisen. We may expect, therefore, to find in the early years of that century much diminution in small-pox prevalence. The history of small-pox in Glasgow in the days of Jenner shews that in the absence

of sanitation, and in the presence of abundance of opportunity for small-pox infection, vaccination enormously reduced the prevalence of variola.

Coming now to statistics in the London Bills of Mortality, the small-pox deaths in the year 1800 were 2400, but subsequently never reached 2000. In the ten years 1771-80, the deaths from small-pox were 20,923; in the next ten years, 17,687; and in the last ten years of the century, 18,477. In the first ten years of the nineteenth century they fell to 12,534, in the second ten years to 7858, and in the third ten years to 6950, though the population within the limits of the Bills had increased from 746,233 in 1801 to 1,180,292 in 1831. The Bills were imperfect, probably more so in the later years than in the earlier, but they shew a striking change as regards small-pox in London.

The best method available for extracting information about small-pox

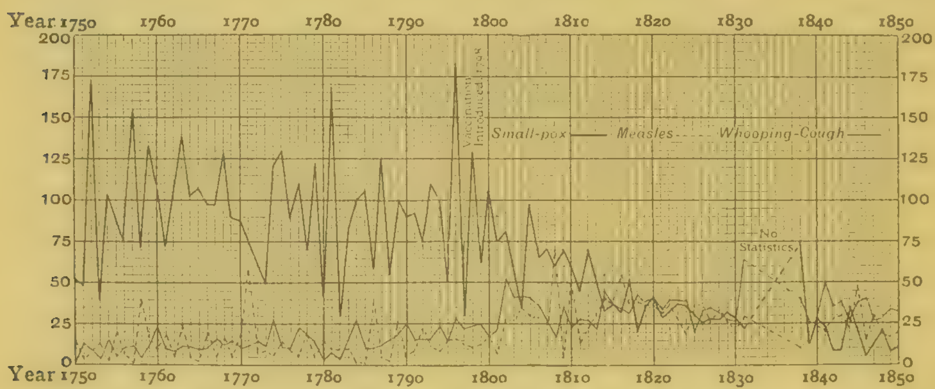


CHART 12.—Death-rates for small-pox, whooping-cough, and measles, 1750-1850.

from the London Bills is to note the proportion which that disease contributes to the total deaths from all causes. This gets rid of the difficulty about the uncertainty of population at any given period, and the imperfection of records just referred to applies to all diseases as well as small-pox. Chart 12 shews the mortality for the century 1750-1850, and, for purposes of comparison, the death-rates for whooping-cough and for measles. Small-pox in prevaccination times, as will be seen later, resembled measles and whooping-cough in being a disease of childhood. The diagram shews how small-pox fell and measles and whooping-cough rose in the fifty years after the introduction of vaccination as compared with the previous fifty years.

We have seen that in 1775, in the town of Chester, 93 per cent of the population had had small-pox at some time or other; and that in 1722, in Ware, 82 per cent of the population had had small-pox. For very few places are there any comparable statistical data relating to the first quarter of the nineteenth century; but in Cambridge, with a total population of 14,142 in 1821, the number of persons who, up to the

summer of 1826, had had small-pox during the preceding twenty-five years was 3560, or about 25 per cent. These figures do not include attacks previous to 1800; but the children born during the twenty-five years referred to were 8112, and of these only 34·4 per cent had had small-pox, including 12·7 per cent by inoculation.

In Glasgow in the ten years 1791 to 1800 the total recorded small-pox deaths were 3302, and in the ten years 1801-10 they fell to 1404. Dr. Robert Watt of Glasgow, writing in 1813, divided the thirty years 1783 to 1812 into five periods of six years each, the last two periods being subsequent to the introduction of vaccination, which was extensively practised in the town. In the three prevaccination periods small-pox contributed to the deaths from all causes the following percentages:—(1) 19·55, (2) 18·22, and (3) 18·70. In the next two periods, when vaccination was being largely used, the contribution of small-pox to deaths from all causes fell to 8·90 and 3·90 per cent. The cases were not isolated, and there was superabundant material to infect all who were susceptible, but some influence had intervened to diminish the small-pox death-rates rapidly and greatly. The agency was not sanitation, for during the periods in question the health conditions of Glasgow, as shewn by contemporary accounts and by the course of other diseases, went from bad to worse.

In Sweden the official figures furnished to Sir John Simon began with the year 1749. From 1776 to 1800 inclusive the average small-pox deaths per million living were 2117·6. In the next twenty-five years, namely 1801-25 inclusive, they were as follows for each successive year:—1801, 2563; 1802, 644; 1803, 611; 1804, 605; 1805, 449; 1806, 613; 1807, 884; 1808, 757; 1809, 1007; 1810, 347; 1811, 291; 1812, 167; 1813, 225; 1814, 126; 1815, 191; 1816, 277; 1817, 96; 1818, 120; 1819, 63; 1820, 55; 1821, 14; 1822, 4; 1823, 15; 1824, 226; 1825, 449. The rise at the end of this period is noteworthy as indicating the need for revaccination. The value of primary vaccination was so fully recognised in Sweden that it was made compulsory in 1816, but the need for revaccination was not then recognised.

In Copenhagen small-pox was very prevalent up to 1801, when it suddenly declined, and even disappeared entirely, there being no recorded deaths between 1810 and 1824. Then it began to prevail again, revaccination having become necessary. The following are the annual small-pox deaths in Copenhagen from 1791 to 1810 inclusive:—297, 155, 139, 452, 248, 357, 423, 386, 54, 35, 486, 73. From 1803 to 1810 the deaths were respectively—5, 13, 5, 5, 2, 46, 5, 4. Then they entirely ceased, and there were absolutely none during the next thirteen years.

These figures indicate the decline of small-pox in Europe after vaccination came to be practised, and before the need for revaccination became an appreciable factor in the case. Sanitation has been spoken of, and its influence will be referred to later, but obviously sanitation cannot account for any such abrupt decline; and we have seen that the difference in the practice of small-pox inoculation is equally inadequate as an explanation. We shall now go on to shew that various other lines of evidence concur

in clinching the conclusion that vaccination is the agency responsible for the decline of small-pox.

The official returns from 1838, when systematic registration of deaths in England and Wales began, to 1890, are given in a table in the Final Report of the Royal Commission. For subsequent years, the figures have been kindly supplied to me by Dr. Tatham of the General Register Office :—

Year.	Estimated Population to the Middle of the Year.	Number of Deaths from Small-pox (with those returned as from Chicken-pox).	Deaths from Small-pox (with those returned as from Chicken-pox) to every 100,000 living.
1891	29,085,819	140	0·5
1892	29,421,392	554	1·9
1893	29,760,842	1,584	5·3
1894	30,104,201	928	3·1
1895	30,451,528	309	1·0
1896	30,802,858	692	2·2
1897	31,158,245	128	0·4
1898	31,517,725	369	1·2
1899	31,881,365	298	0·9
1900	32,249,187	212	0·7
1901	32,621,263	471	1·4
1902	32,997,626	2,587	7·8
1903	33,378,338	876	2·6

It will be noted that these figures include deaths from chicken-pox, but there is little chance of a death registered from chicken-pox being due to small-pox. Chicken-pox resembles only much modified small-pox, which is not a fatal disease. The subject is fully discussed in my evidence before the Royal Commission on Vaccination, Sixth Report, pp. 345-346 and 348-351.

Grouping the figures from 1848 to 1903, and stating them for age-periods, we get the following :—

ENGLAND AND WALES

Annual Death-Rates from Small-pox per Million Living, 1848-1903

	Under 5.	5-10.	10-15.	15-25.	25-45.	45 and Upwards.
1848-54	1514	323	91	110	69	24
1855-64	788·8	209·5	68·7	118·9	87·8	36·2
1865-74	782·5	333·2	142·3	267·2	220·7	87·5
1875-84	127·8	62·9	46·4	82·4	76·6	33·9
1885-94	50·2	14·9	11·1	24·0	31·6	19·0
1895-1903[1]	31·2	12·6	7·3	10·1	20·9	17·5

[1] Nine years.

The decline in the last period is largely due to lowered fatality of the disease, the epidemic type having in the main been very much milder than in the previous groups of years.

Vaccination was introduced in the beginning of the nineteenth century, the National Vaccine Establishment was endowed in 1808, gratuitous vaccination of the poor was provided from local rates in 1840, and the first obligatory law was passed in 1853. Boards of Guardians were empowered to appoint vaccination officers by the Act of 1867, such appointments were made compulsory by the Act of 1871, and various changes in the law, including the introduction of an exemption clause, were made in the Act of 1898. The table shews how at all ages small-pox has declined since vaccination began, and attention will subsequently be called to the different rate of diminution at different periods of life, but certain special illustrations of the influence of vaccination will now be given.

Small-pox Attack-Rates among the Vaccinated and Unvaccinated.—The total relative proportions of the vaccinated and unvaccinated in the communities is sufficiently known to allow of a broad comparison between the attack-rate of the disease amongst the vaccinated and unvaccinated respectively. Small-pox hospitals are open alike to vaccinated and unvaccinated, and hospital treatment of small-pox is now so general that the proportions of the two classes admitted to hospital may usefully be compared with their proportions in the relative communities. These comparisons are subject to one important reservation. Infantile vaccination, as we shall see, does not give permanent protection against small-pox attack,[1] and revaccination is so incompletely carried out in this country that attack-rates are very much higher than if it were practised even to the same incomplete extent as primary vaccination.

Between 1873 and 1884 Dr. W. Gayton at Homerton Small-pox Hospital had charge of 10,403 small-pox cases. Amongst these he found that the admissions under ten years old were 2493, of whom 1187 were unvaccinated and 1306 were "vaccinated," the latter term including all degrees of vaccination and even those said to have been vaccinated but without any marks of the operation. The unvaccinated, therefore, were 47·6 per cent of the total. At Fulham Hospital Dr. Sweeting reported that between the years 1880 and 1885, of 370 children under ten 168, or 45·4 per cent, were unvaccinated. These figures refer to a time when the London vaccination default was less than 10 per cent, so that the unvaccinated children yielded in proportion to their numbers five times as many small-pox cases as the vaccinated.

But one hospital in London had a different and exceptional experience, which is of special interest. The "London Small-pox Hospital" was founded in 1746, and continued to exist after the Metropolitan Asylums Board's hospitals were established. It was not a rate-supported institution, but received paying patients from a better class of the community.

[1] It gives more prolonged protection against death by small-pox than against attack. See p. 780.

For many years before its wards at Highgate were closed, it accepted no patients under seven years old, and, therefore, excluded the period of life most under the influence of vaccination. In these circumstances the proportion of vaccinated patients admitted to hospital was as high as 93 per cent, and in 1888-91 every one of fourteen cases admitted had been vaccinated. This hospital therefore was the exception which proved the rule.

In his report to the Royal Commission upon London small-pox outbreaks in 1892-93, Dr. A. P. Luff stated that of 2353 cases at all ages about which he obtained information there were 409 unvaccinated persons, or 17·3 per cent. Under ten years of age there were 358 attacks, and of these 228 were unvaccinated, or 63·7 per cent. From 1872 onwards the neglect of vaccination did not nearly amount to 17 per cent, much less 63 per cent.

Small-pox Attack-Rates amongst the Vaccinated and Unvaccinated in Houses invaded by the Disease.—Another illustration of the influence of vaccination in checking small-pox prevalence is to be found in the data ascertained as to the attack-rate of the disease on the vaccinated and unvaccinated inmates of houses actually invaded by small-pox. The data are recorded in the Report of the Royal Commission, and they constitute a control experiment which is practically beyond serious criticism, and is, indeed, hardly open even to quibbling comment. Inquiries on the lines indicated were instituted, not merely in towns like Sheffield where infantile vaccination had been well attended to, and where it might be alleged that the unvaccinated included an appreciable proportion of sickly children certified unfit for the operation; the investigations refer also to Dewsbury, Leicester, and Gloucester, centres of anti-vaccination, where the unvaccinated could not be regarded as "quality as well as a quantity" excepting in this sense, that according to the views of anti-vaccinists those who declined vaccination in these towns would be a specially intelligent population, giving due heed to the health of their children, whilst the children themselves, inasmuch as they had not been subjected to the health-destroying Jennerian rite, would be in an exceptionally good position to resist attack by small-pox. The vaccinated and unvaccinated inmates of the invaded houses were in other respects in the same position as regards exposure to infection and ability to resist it. They breathed the same air, ate the same food, lived in the same domestic and municipal environment, attended the same schools, or were engaged in similar occupations, and were equally exposed to infection from existence of the disease in their own dwellings. The sole difference was that some were vaccinated and some were unvaccinated. In these circumstances what heed did small-pox give to the vaccinal condition of the inmates? The answer is unequivocal. In Warrington, of 2535 persons living in invaded households 688 were under ten years old. Of these 633 were vaccinated and 55 unvaccinated. Of the 633 vaccinated, 28 were attacked, or 4·4 per cent. Of the 55 unvaccinated, 30 were attacked, or 54·5 per cent. In ill-vaccinated

Dewsbury, in 544 invaded houses regarding which information was obtained, the number of the vaccinated under ten years old was 408, and of these 42 were attacked, or 10·2 per cent, while the unvaccinated of the same age amounted to 311, and of these 158 were attacked, or 50·8 per cent. In still less vaccinated Leicester, in invaded houses reported on by Dr. Sidney Coupland, the vaccinated child population was 78, with 2 attacks, or 2·5 per cent of the total, while the unvaccinated child population was 283, with 100 attacks, or 35·3 per cent of the total. In Gloucester, where neglect of vaccination was notorious for years before small-pox came and left the town the best vaccinated in the British dominions, information was obtained regarding 899 invaded houses out of a total of 1097. The total vaccinated population under ten years old in these was 272, and the attacks were 24, or 8·8 per cent, while the total unvaccinated child population was 1331, and the attacks were 617, or 46·3 per cent.

All these figures refer to children under ten years of age. Above that age the contrast between vaccinated and unvaccinated is not nearly so great, because the protective power of vaccination against attack by small-pox has diminished, and the time for revaccination has come. Yet even over ten years of age primary vaccination retains a very appreciable protective influence against attack (still more so against death) as will be seen by the figures in the following table :—

	Attack-Rate under Ten.		Attack-Rate over Ten.	
	Vaccinated.	Unvaccinated.	Vaccinated.	Unvaccinated.
	Per cent.	Per cent.	Per cent.	Per cent.
Warrington . . .	4·4	54·5	29·9	57·6
Dewsbury . . .	10·2	50·8	27·7	53·4
Leicester . . .	2·5	35·3	22·2	47·6
Gloucester . . .	8·8	46·3	32·2	50·0

Even among persons over ten years of age, therefore, the vaccinated still possess a great advantage over the unvaccinated in the matter of resistance to small-pox attack. The total cases on which these rates are based cannot be criticised as insufficient to yield reliable results. In the invaded houses enumerated in Warrington the vaccinated population was 2387 and the unvaccinated 107. In Dewsbury there were in the invaded houses 2315 persons vaccinated (including cases of alleged vaccination) and 605 unvaccinated persons (including those "under vaccination"). In Leicester the similar figures were 841 for the vaccinated and 388 for the unvaccinated, and in Gloucester in the enumerated houses the vaccinated numbered 3386 and the unvaccinated 1475.

Other special illustrations of the protective effect of vaccination are to be found in the experience of particular classes of the population, amongst whom vaccination is specially practised—such as the postal

service, the army and navy, and small-pox nurses—but this evidence comes in more conveniently when discussing revaccination (*vide* p. 787).

The Age-Incidence of Small-pox.—Under this heading some of the most important evidence is found of the power of vaccination to prevent small-pox. In the history of epidemic disease there is perhaps nothing more striking than the remarkable change which has taken place in the age-incidence of small-pox. In prevaccination times small-pox was a disease of childhood just as much as whooping-cough and measles were and are. As in whooping-cough and measles so in small-pox, some difference no doubt existed in age-incidence as between town and country communities, opportunities for infection being more frequent in the former than in the latter, and the age-incidence being correspondingly lower. In country districts having little traffic with the outside world, opportunity for infection might be deferred until adult life, and in towns, therefore, where population was appreciably increased by rural immigration, among these immigrants there would often be adult cases of small-pox, and even amongst the town-born, small-pox attack might occasionally be deferred till late in life, just as we find to be the case with measles, scarlet fever, and whooping-cough.

The earliest available statistics of age-incidence relate to the town of Geneva, and refer to the long period of 180 years from 1580 to 1760. The figures are so remarkable that they are here given in full, and are as follows:—

GENEVA, 1580-1760

Small-pox Deaths at various Ages, 25,349

		Years.	
6792	in age class	0-1 = 26·8	per cent of the total.
5416	,,	1-2 = 21·4	,,
4116	,,	2-3 = 16·2	,,
2826	,,	3-4 = 11·1	,,
1928	,,	4-5 = 7·6	,,
1325	,,	5-6 = 5·2	,,
944	,,	6-7 = 3·7	,,
543	,,	7-8 = 2·5	,,
454	,,	8-9 = 1·8	,,
345	,,	9-10 = 1·4	,,
267	,,	10-15 = 1·0	,,
141	,,	15-20 = 0·6	,,
87	,,	20-25 = 0·3	,,
48	,,	25-30 = 0·2	,,
17	,,	above 30 = 0·1	,,

The small-pox deaths recorded in the above table amounted to a total of 25,349. Of these 26·8 per cent were under one year of age, and 56·3 per cent were between one and five years, whilst only 2·2 per cent of the the total were over ten years old.

In Kilmarnock a register of burials was kept from 1728 to 1764

inclusive, and the ages and causes of death are stated. The total small-pox deaths were 622, and no less than 98·8 per cent of these were under ten years old. Of the 622 there were under one year 118, between one and two years 146, between two and three years 136 cases, between three and four years 101, between four and five years 62, and between five and six years 23. In an epidemic in Chester in 1774 there were 202 deaths, not one of the cases being over ten years old, and 51 being less than one year old. Without going further into detail as to prevaccination times it may be enough to state that in a total of 36,755 small-pox deaths at all ages occurring in Kilmarnock, Edinburgh, Manchester, Warrington, Chester, Geneva, and the Hague, in various prevaccination periods from 1580 onwards, 17,252 were under two years old. In Berlin, Dr. Edwardes notes that in seventeen years, 1758-74, of 6705 small-pox deaths only 45 were over fifteen years old, and in the Prussian county Wernigerode, in 1796, of 817 small-pox deaths only 30 were over ten years old, and only 1 over fifteen years old.

The reason why small-pox so rarely attacked adults is obvious. At all ages above childhood the population consisted practically of persons who had been attacked by small-pox, and had perhaps been disfigured or permanently injured, but who yet had been left alive to enjoy the protection obtained at whatever cost. Even then immunity was not absolute, but it was very great.

Small-pox being originally a disease of childhood, the influence of vaccination on its age-incidence in modern times must now be considered. That influence is twofold. In the first place, by reducing the number of persons susceptible to attack in any given population it reduces the chance of small-pox epidemics being established, and by lengthening the intervals between epidemics it raises the general age-incidence of the disease. This result applies also to the unvaccinated. Secondly, by rendering the once vaccinated insusceptible to attack by small-pox for a varying number of years after the performance of the operation, it raises the incidence of the disease amongst those ultimately attacked to a much higher range of ages than amongst the unvaccinated. We therefore expect to find in the first place that, taking the nation as a whole, including the unvaccinated, the age-incidence will be considerably higher than in prevaccination times; secondly, that though under the protection given to whole communities by vaccination even the unvaccinated are benefited, yet there will remain an obvious difference between the age-incidence of the disease amongst them as compared with the vaccinated and revaccinated. The following table, taken up to 1894 from the Royal Commission's Report, and for subsequent years from figures kindly supplied to me by Dr. Tatham of the General Register Office, justifies the first expectation. It shews for successive quinquennia from 1848 to 1903 [1] the distribution into various ages of 1000 small-pox deaths at all ages:—

[1] The last period only includes four years.

England and Wales

Deaths from Small-pox at certain Age-Periods to 1000 Deaths from Small-pox at all Ages

	1-5.	5-10.	10-15.	15-25.	25-45.	45 and Upwards.
1848-54	677	130	33	75	67	18
1855-59	559	144	37	117	112	31
1860-64	550	108	42	123	133	44
1865-69	545	103	33	126	145	48
1870-74	312	140	58	200	224	66
1875-79	241	113	72	218	266	90
1880-84	235	98	68	216	286	97
1885-89	191	54	51	229	344	129
1890-94	283	50	26	131	338	172
1895-99	263	132	26	107	332	140
1900-1903	197	64	51	119	349	220

Concerning this table it is necessary to be quite clear on one point. It gives no indication either of increase or decrease of small-pox prevalence. The figures refer solely to the distribution among different periods of life of every 1000 deaths from the disease at all ages. In every line, therefore, the figure 1000 has to be reached, and diminution of one age-period must be counterbalanced by increase at another age-period. The decrease in small-pox mortality since 1848 has been shewn for different age-periods in the table at p. 772.

The earliest period of years in the present table, namely 1848-54, was not under the influence of the Vaccination Act of 1853. Before 1853 there had been much vaccination, but the average age at which the operation was performed would be much higher than after the passage of the obligatory Act, though, from the want of any sufficient machinery for its administration, that Act left much to be desired. In the years 1848-54, of 1000 deaths from small-pox, the number under five years old was 677, as contrasted with the 831 in the Geneva table at p. 776. Thus, a very perceptible difference had already occurred. Under the influence of the successive Acts of 1853, 1867, and 1871 the vaccination of infants was more and more attended to, and the table shews that the proportion of small-pox attacks under five years of age steadily diminished up to 1889. Then a curious phenomenon becomes observable. In the decade 1890-99 there is a definite rise in the proportion of small-pox borne by children under five and ten years old, and in 1900-1903 it occurs in the age-period 10-15 years. This rise is only what might have been expected in presence of increasing neglect of infantile vaccination prior to the passing of the Vaccination Act of 1898. Under that Act infantile vaccination has again increased, and infantile share of small-pox has again diminished.

Small-pox Age-Incidence in the Vaccinated and Unvaccinated.—As

already explained, the table on p. 778, shewing alteration of age-incidence, includes both vaccinated and unvaccinated. It is necessary now to see what are the facts regarding the vaccinated as distinguished from the unvaccinated. In the Local Government Board's Report for 1884 some figures were given with regard to London in that year, and as they can seldom be similarly obtained they should be noted. At that time, of 1000 deaths from small-pox among the vaccinated and unvaccinated jointly, 343 were under ten years old. But in 1000 unvaccinated the number under ten years was 612, whilst among 1000 vaccinated it was only 86. The 612, as contrasted with the Geneva 961 and the Kilmarnock 988 of prevaccination times, indicates roughly the benefit which the unvaccinated had received from the practice of vaccination. The figure 86, as contrasted with 988 and 961, indicates the boon conferred on the vaccinated by their personal protection. Had all the population been vaccinated in the first months of life the figure would have been even lower than 86, as those of the vaccinated whose insusceptibility to attack had already diminished would have had less opportunity of receiving infection if they had been living in the midst of an entirely vaccinated population.

Age-Incidence in Certain Epidemics.—The distinction may be exemplified in a different fashion; the material for this was well brought out by the Royal Commission on Vaccination. Epidemics occurring in six populations, differing greatly with regard to vaccination default, were investigated by them. In Warrington and Sheffield the default in antecedent years had been very slight, and the percentages of total small-pox borne by children under ten years of age in these two towns were 22·5 and 25·6 respectively. In London in the years 1883 to 1891 vaccination default had been greater, amounting to about 10 per cent. In London, accordingly, children under ten years old bore a higher proportion of the total small-pox, namely, 36·8 per cent. In Dewsbury, from 1882-92 the vaccination default was 32·3 per cent, and when small-pox struck the town the children under ten constituted 51·8 per cent of the total cases. In Gloucester anti-vaccination had become increasingly and remarkably popular in the ten years preceding the epidemic. The default had grown from 10·6 in 1885 to not less than 85·1 in 1894. Then the epidemic came, and the children under ten bore 64·5 per cent of the total attacks in the town. In Leicester the default had not climbed so high as 85·1 per cent, but it had been steadier than in Gloucester, so that from 43·8 per cent in 1883 it had reached 80·1 per cent in 1892, and in that town the children bore 71·4 per cent of the total outbreak.[1]

Still another illustration of the manner in which age-incidence is influenced by vaccinal condition is to be found in statistics of small-pox amongst infants. In Scotland, where the Compulsory Vaccination Act dates from the year 1863, the compulsory age is six months. The first

[1] Deducting three deaths which occurred among children in a scarlet fever ward through proximity to the small-pox hospital, the proportion left is 66·6 per cent, not 71·4.

half-year of life, therefore, is the period which is not under the influence of the Act. In the nine years, 1855-1863, prior to the Vaccination Act children under six months old had amongst them 139 deaths out of every 1000 occurring at all ages. In the years 1864-1887, that is the twenty-four years subsequent to the passing of the Act, children under six months old still bore 138 of every 1000 small-pox deaths. The Act had practically no effect on them. The second half-year of life is the first age-period under the influence of the law of 1863. In the nine years prior to the Act they had borne 153 of every 1000 small-pox deaths, and in the twenty-four years subsequent to it their share was only 47. These figures are capable of no other interpretation than that vaccination made the difference. In the first quinquennium of life in the nine years 1865-1873, there were 413 of every 1000 small-pox deaths, while in the twenty-four years 1864-1887, there were only 137. The total actual small-pox deaths occurring in these two periods were in the nine prior years 8807, and in the twenty-four subsequent years 9240.[1] The totals, therefore, are sufficiently large to make the conclusions statistically reliable.

Yet another instance of the same truth may be mentioned. In Germany the compulsory vaccination age is in the second year of life, so that the first two years may be taken for the control experiment here. And as recorded by Dr. Sweeting, the returns of the Imperial Health Office shew that in the five years 1886-1890, of 735 small-pox deaths at all ages, 301, or 41 per cent, were under two years old. In the same five years in England and Wales, in 1846 deaths from small-pox at all ages, 219 were under one year old and 43 between one and two years, so that the percentage under two years was only 14·19. In view of statistics like these, no other explanation of the altered age-incidence of small-pox is feasible than that its cause is to be found in vaccination.

Fatality of Small-pox.—Long after infantile vaccination has ceased to give absolute protection against attack by small-pox, it continues to give a large degree of protection against death by small-pox. It has a modifying as well as a preventive influence. To prove this it is necessary to refer to the case-mortality of small-pox in its relation to vaccination. As with regard to age-incidence, so with regard to case-mortality, it would be most important to ascertain the facts for prevaccination times. Unfortunately this appears to be practically impossible. The fatality of natural small-pox is very high in the first years of life, and decreases quickly until its minimum is reached in the age-period of 10-15 years, after which it rises again. No statement of case-mortality for any particular small-pox outbreak is therefore of much value unless the age-incidence of the disease in that particular outbreak is known, and it happens that, so far, hardly any statistics have come to light giving information on both points.

Some figures exist for the village of Aynho in Northamptonshire, and for the various age-periods there the case-mortality quite coincides with what is often experienced among the unvaccinated in the present

[1] From this figure 59 should be deducted for chicken-pox.

day, namely, a high mortality at the earliest ages, a low mortality in youth, and a high fatality in later life. But the total cases at Aynho were only 132, and the age-distribution is so peculiar in respect of the very small number under five years and the entire absence of cases under two years, that Aynho cannot be relied on for any general conclusions. Dr. Jurin, then Secretary to the Royal Society, collected some statistics relating to certain towns in Yorkshire in certain years between 1720 and 1730, and the fatality-rate given is about 16·5 per cent; but unfortunately the ages are not stated, and there is, in my opinion, much reason to doubt whether small-pox deaths occurring in the first two years of life are included. Bernouilli stated that in young children one-third died (Edwardes). It is obvious, however, that in prevaccination times small-pox varied greatly in severity of type. Dr. Wagstaffe wrote that there is a kind of small-pox which a doctor cannot cure and another kind which a nurse cannot kill. Not only did the fatality vary as between case and case but also as between epidemic and epidemic. There is evidence that the deaths were occasionally as few as 1 in 40, and sometimes as many as 1 in 3, or 2 in 5. In the London Small-pox Hospital in 1746-63 the fatality-rate was 25·3 per cent, and in the last twenty-five years of the eighteenth century it was 32 per cent. Dr. Edwardes notes that in 1781 there were in the hospital 257 deaths in 646 cases, or 40 per cent. The records of the Danish Government state that in Iceland in 1707, in a population of about 50,000, there were 18,000 deaths. This is probably an example of an outbreak in a community which had been for many years unvisited by the disease, and even if we take the almost impossible view that every individual was attacked in 1707, the fatality-rate in the population of 50,000 would be 36 per cent, but it is practically certain to have been considerably higher.

Perhaps, however, the fatality-rate of natural small-pox in the unprotected in the eighteenth century may have been lower than in the nineteenth. Looking to the ravages of the disease in prevaccination times, it is reasonable to suppose that a very large proportion of the population of the eighteenth century must have been the descendants of those who had been able to resist death by small-pox. But protection by variolation in the second half of the eighteenth century, and by vaccination in the nineteenth, must have preserved from fatal small-pox a large part of the specially susceptible population of these times, whose offspring might inherit their susceptibility, and when small-pox did return after long intervals, the unprotected population might manifest a greater average liability to death than before. This, however, is very speculative, and the fact remains that we can make no useful comparison of the fatality-rate of small-pox in the eighteenth century with that of the unvaccinated in the nineteenth century, so we are now practically confined to comparisons between the fatality of the disease among the vaccinated and unvaccinated in modern epidemics.

As in the eighteenth century so in the nineteenth, and already in the

twentieth the type of small-pox has differed in different epidemics. In the pandemic of 1870-74 it was severe, and the fatality-rate was high. Within the last decade, on the contrary, there has been in America, Trinidad, and elsewhere, a remarkably mild type of small-pox, and in our own country some approach to that type has now been manifested. The American outbreak, indeed, brings to mind a "sport" of small-pox which existed in Gloucestershire in 1789, and was much studied by Jenner and one of the medical societies of which he was an active member. Jenner had not yet begun vaccination, and he discussed the question whether the much modified small-pox of the then existing epidemic might not be used as a source of future small-pox inoculation, so as to set up an even milder disease than resulted from inoculation according to the methods which had been introduced by the Suttons, Dimsdale, and others. Dr. Adams of the London Small-pox Hospital in the year 1806 reported on a similar mild variolous disease which at that time was known by the name of pearl-pox.

Leaving these questions and coming now to the ascertained facts regarding the fatality of small-pox in the vaccinated and unvaccinated, the statistical material is superabundant. At the London Small-pox Hospital in nearly 6000 cases, in 1838 to 1865, as recorded by Mr. Marson, the fatality amongst the unvaccinated was 35·5 per cent, and in the vaccinated 8·7 per cent. Dr. W. Gayton in his digest of over 10,000 cases treated by him in the metropolitan hospitals found that among 2169 unvaccinated persons there were 938 deaths, or 43 per cent, and among 8234 vaccinated persons, including all doubtful cases, there were 869 deaths, or 10·5 per cent. In Fulham Hospital in 1880-85, Dr. Sweeting found that in 358 unvaccinated cases there were 165 deaths, or 46 per cent, and that in 2226 vaccinated cases, including even those who were only said to be vaccinated but bore no marks, there were 263 deaths, or 11·4 per cent. In the hospitals of the Metropolitan Asylums Board in 1901-2 there were treated 9659 cases of small-pox, with 1629 deaths. Among 6945 vaccinated cases, including all degrees of vaccination and all ages of patients, there were 705 deaths, or 11·5 per cent. In 2278 unvaccinated cases there were 753 deaths, or 33·1 per cent. The "doubtful" cases were 436 with 171 deaths, and these may be added either to vaccinated or unvaccinated without seriously altering the fatality-rates. In Belvidere Hospital, Glasgow, in 1900-1 there were 122 unvaccinated cases with 63 deaths, or 51·6 per cent, and 1688 vaccinated, including all doubtful cases, with 175 deaths, or 10·4 per cent. But it has already been pointed out that, in the matter of small-pox fatality, the ages of the attacked must be noted. Dividing Dr. Gayton's total patients according to their ages, and still retaining in the vaccinated class all who were alleged to have been vaccinated, or who had any marks of vaccination no matter how trivial, the following were the comparative rates of the vaccinated and the unvaccinated :—

Age.	Unvaccinated.	Vaccinated, including good marks, imperfect marks, and all alleged to be vaccinated but without any evidence of vaccination.
	Per Cent.	Per Cent.
0–2	66	20·7
2–5	50	18·4
5–10	35	7·3
10–15	23	4·9
15–20	42	6·4
20–25	48	11·9
25–30	53	15·2
30–40	41	17·4
40–50	43	20·0
50 and upward	43	27·5

In the Metropolitan Asylums Board hospitals in 1901-2, for which the all-age figures are given above, there were 134 attacks among vaccinated persons under ten years old, and only 2 of these died, or 1·5 per cent. Amongst the unvaccinated, the cases under ten years old were 1274, and the deaths 442, or 34·7 per cent.

The figures already given for Belvidere Hospital, when divided according to ages, are as stated in the following table, in which once more all "doubtful" cases are included among the vaccinated :—

Glasgow Epidemic, 1900-1901

Small-pox Fatality-Rate, at different Age-Periods, in the Unvaccinated as compared with the Vaccinated (including all "doubtful" cases)

Age.	Unvaccinated.			Vaccinated.		
	Cases.	Deaths.	Mortality.	Cases.	Deaths.	Mortality.
			Per Cent.			Per Cent.
0–5	54	36	66·6	6	1	16·6
5–10	12	2	16·6	33	...	...
10–15	14	4	28·6	95	2	2·1
15–20	6	2	33·3	133	1	0·7
20–25	6	4	66·6	257	14	5·4
25–35	11	5	45·5	639	51	7·9
35–45	12	4	33·3	353	57	16·1
45–55	7	6	85·7	124	30	24·2
55–65	...	...	...	33	14	42·4
65 and over	...	...	...	15	5	33·3
All ages	122	63	51·6	1688	175	10·4

Coming next to the epidemics investigated on behalf of the Royal Commission, similar information is contained in the Final Report. In London, in 1892-93, 110 vaccinated children under ten years of age were

attacked by small-pox and none died. If to these be added 20 of the "doubtful" class with 6 deaths, the percentage becomes 4·6. Of a similar age 228 unvaccinated were attacked and 61 died, or 26·7 per cent. Of the vaccinated over ten years old 1643 were attacked and 39 died, or 2·3 per cent. If all "doubtful" cases be added to these, the attacks become 1814 with 77 deaths, or 4·2 per cent, whilst among 181 unvaccinated 38 died, or 20·9 per cent. In the Dewsbury epidemic of 1891-92, of 44 vaccinated children under ten 1 died, or 2·2 per cent, and of 174 unvaccinated children 56 died, or 32·1 per cent. Over ten years old, of 577 vaccinated persons 15 died, or 2·6 per cent. If to these be added 24 persons alleged to be vaccinated of whom 2 died, the figures become 601 attacks with 17 deaths, or 2·8 per cent, whilst of 192 unvaccinated 36 died, or 18·7 per cent. The unvaccinated here include those described as "under vaccination," and their inclusion rather lowers the fatality-rate. In the Warrington outbreak, of 33 vaccinated children under ten, 2 died, or 6 per cent, and of 32 unvaccinated 12 died, or 37·5 per cent. Of 560 vaccinated persons over ten years old 36 died, or 6·4 per cent, and of 36 unvaccinated persons 12 died, or 33·3 per cent. In the Leicester epidemic of 1892-93, 2 vaccinated children under ten were attacked and both recovered. Of unvaccinated children 107 were attacked and 15 died, or 14 per cent; of vaccinated persons over ten, 197 were attacked and 2 died, or 1·0 per cent, and of the unvaccinated 51 were attacked and 4 died, or 7·8 per cent. In the Gloucester epidemic 26 vaccinated children under ten years old were attacked and 1 died, or 3·8 per cent, whilst 680 unvaccinated children were attacked and 279, or 41 per cent, died. Of vaccinated persons over ten years old 1185 were attacked and 119 died, or 10 per cent, and of the unvaccinated of similar age 88 were attacked and 35 died, or 39·7 per cent.

Taking the six towns referred to in the Royal Commission's Report the total number of children attacked under ten years old was 2038, of whom 539 died, or 26·4 per cent. Of this total 1449 were recorded as unvaccinated, of whom 523 died, or 36 per cent. The remainder, consisting of the vaccinated, amounted to 589, with 16 deaths, or 2·7 per cent. Over ten years of age the total attacks were 9001, with 744 deaths, or 8·2 per cent. Of these 870 are classed as unvaccinated, with 299 deaths or 34·3 per cent, leaving for the vaccinated 8138 attacks with 445 deaths or 5·4 per cent.

It will be seen throughout these figures that the difference in the fatality-rate is much greater between the vaccinated and the unvaccinated under ten years of age than over that age. The explanation is obvious. Over that age vaccination had lost more or less of its protective power.

Sufficient and Insufficient Vaccination.—The degree of protection conferred by vaccination corresponds in great measure to the thoroughness with which the operation has been performed. Statistics in support of this proposition are well known. Mr. Marson of the London Small-pox Hospital was the first to deal in detail with the subject, and his figures led to conclusions which have since his time been confirmed in

every considerable epidemic of small-pox. His results were placed before the Royal Commission in a table handed in by Sir Richard Thorne. The table is as follows :—

Cases of Small-pox classified according to the Vaccination marks borne by each Patient respectively.	Percentage of Deaths in each Class respectively, uncorrected.[1]		Percentage of Deaths in each Class respectively, corrected.[1]	
	1836-51.	1852-67.	1836-51.	1852-67.
1. Stated to have been vaccinated, but having no cicatrix	25·5	40·3	21·7	39·4
2. Having one vaccine cicatrix .	9·2	14·8	7·6	13·8
3. Having two vaccine cicatrices .	6·0	8·7	4·3	7·7
4. Having three vaccine cicatrices .	3·6	3·7	1·8	3·0
5. Having four or more vaccine cicatrices	1·1	1·9	0·7	0·9
Unvaccinated	37·5	35·7	35·5	34·9

The cases on which these figures were based were 3094 in the period 1836 to 1851, and 10,661 in the period 1852 to 1867.

Dr. Gayton's complete table, which has already been referred to, is as follows :—

Ages.	Vaccinated. Good Marks.			Vaccinated. Imperfect Marks.			"Vaccinated," but no evidence of Vaccination			Not Vaccinated.		
Years.	Cases.	Deaths.	Per Cent.	Cases.	Deaths.	Per Cent.	Cases.	Deaths.	Per Cent.	Cases.	Deaths.	Per Cent.
0–2	4	0	0	32	3	9	22	9	41	276	181	66
2–5	57	0	0	150	18	12	96	38	40	401	202	50
5–10	206	2	1	532	27	5	207	40	19	510	180	35
10–15	439	5	1	939	32	3	214	42	20	317	74	23
15–20	606	12	2	1037	66	6	205	39	19	204	86	42
20–25	389	11	3	843	100	13	167	56	34	174	83	48
25–30	189	12	6	529	80	15	116	35	30	105	56	53
30–40	147	14	10	526	78	15	137	49	36	103	42	41
40–50	29	4	14	186	33	18	85	24	28	49	21	43
50 +	19	2	11	80	18	22½	46	20	43	30	13	43
All ages.	2085	62	3	4854	455	9	1295	352	27	2169	938	43

In Glasgow, for the epidemic of 1871-72, Dr. Russell illustrated the same truth in a diagrammatic form, which has often since then been used for the exhibition of similar facts. The chart is reproduced here :—

[1] The terms *uncorrected* and *corrected* are used to signify the inclusion or exclusion of those fatal cases of small-pox in which the patient suffered from some other disease superadded to the small-pox.

The reporters to the Royal Commission give similar facts relating to the epidemics in the various towns. Apart from Mr. Marson's cases, the total number analysed by the Commission is 6839, and, dividing these

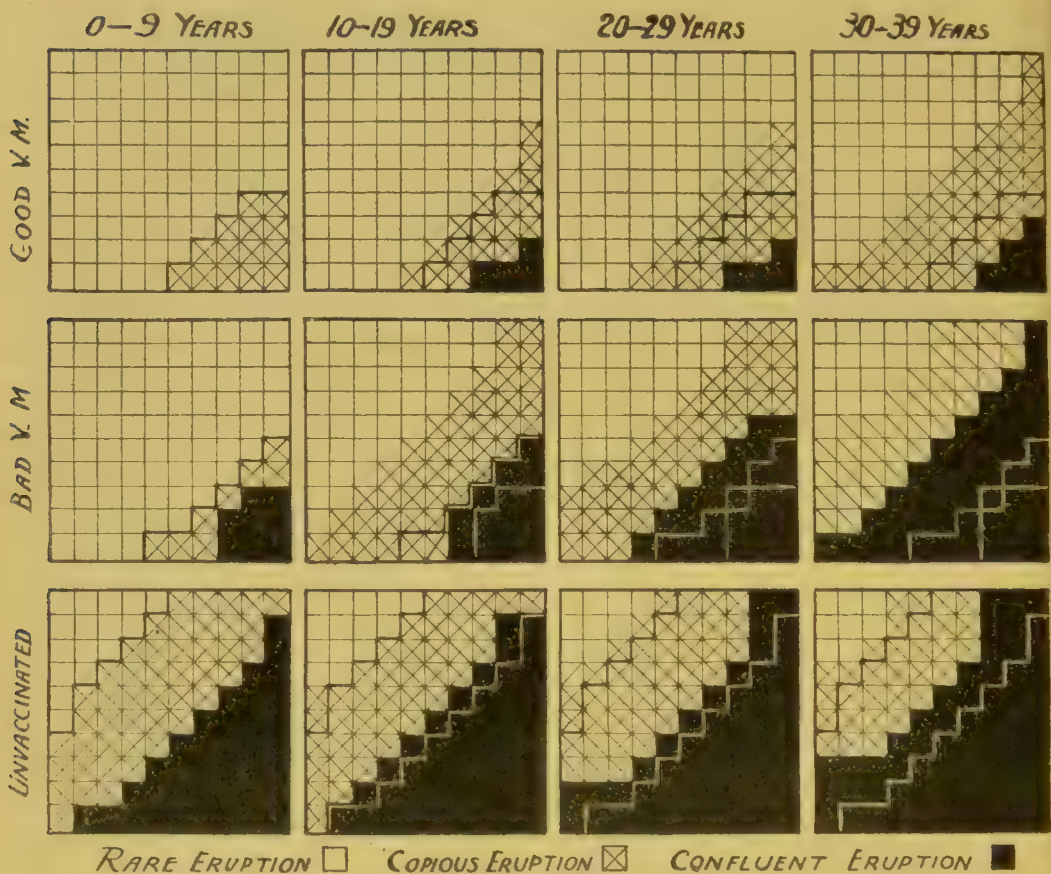


CHART 13.—The large squares contain 100 smaller ones, so that the varieties of the smaller squares represent percentages. ("V.M." means vaccination marks. The thicker black-and-white lines indicate the original percentages at 0-9 years.)[1]

into classes according to the number of marks, the following is the result:—

1 mark,	1357 cases,	with	85 deaths,	or 6·2	per cent.
2 marks,	1971	,,	,, 115	,, 5·8	,,
3 ,,	1997	,,	,, 75	,, 3·7	,,
4 ,,	1514	,,	,, 34	,, 2·2	,,

In Belvidere Hospital, Glasgow, in 1900-1901, there were treated the following small-pox cases:—

[1] This diagram is reproduced from *Public Health Administration of Glasgow*, a memorial volume of Dr. Russell's writings, 1905.

Vaccination Scars.	Total Cases.	Confluent and Hæmorrhagic.	Deaths.
One . . .	886	177 or 20 per cent	101 or 11·4 per cent
Two . . .	589	83 ,, 14·1 ,,	44 ,, 7·3 ,,
Three . . .	94	13 ,, 13·8 ,,	4 ,, 4·2 ,,
Four . . .	74	9 ,, 12·2 ,,	2 ,, 2·8 ,,

Very fully elaborated statistics, teaching an essentially similar lesson, are given in a series of tables in the Metropolitan Asylums Board's Report for 1902.

Similar results are obtained on the basis of measurement of area of marks instead of number of marks, but it is obvious that figures with regard to number also broadly include area. The standard required from public vaccinators by the Local Government Board is a total area of not less than one half of a square inch. A curious criticism has lately been made with regard to facts like these. It has been held by one or two reputable authorities that exceptional susceptibility to the local effects of vaccination may be conjoined with exceptional susceptibility to small-pox. The suggestion has, therefore, been made by opponents of vaccination that a large area of marks should be accompanied by severity instead of mildness of small-pox attack. But obviously, on any skin, four insertions of lymph will produce a larger area than one or two insertions of equal size, and the greater the area of insertion in any individual case the greater will be the mark left, though some individuals may shew a larger scar than others from insertions apparently equal in extent.

The difference between sufficiency and insufficiency of vaccination is manifested in the earlier return of susceptibility to small-pox infection. Immediately after the vaccinal process is completed, if the local result itself has been characteristic, whether the area of insertion has been large or small, or the number of marks has been one or four, the individual is protected against small-pox, and the limited degree of protection resulting from insufficient vaccination manifests itself only as time passes.

Revaccination.—Evidence of the value of revaccination as compared with a single vaccination performed in infancy is similar in nature, and in modern times equal in amount, to that of the value of a single infantile vaccination as compared with non-vaccination.

The mistake of Jenner's life was that he failed to recognise the want of permanence of the protection from small-pox which is conferred by primary vaccination. His *Inquiry* was published in 1798, and he died in 1823, but throughout that quarter of a century he never altered his view. His failure to realise the truth is not so surprising when all the facts are considered. He rightly regarded vaccinia as variola of the cow, and throughout all his researches he was guided by that conviction. He admitted no difference in degree between the protection afforded by a mild attack of small-pox and that afforded by a severe attack, whether the severity belonged to the natural or the artificial (inoculated) disease, and, following this line, he saw no differ-

ence between the protective power of human small-pox as manifested by its ordinary eruption and that of cow-pox as shewn by the vaccine vesicle on an infant's arm. He often pointed out, in explanation of vaccine failures, that one attack of small-pox did not invariably protect against a second, but he did not regard such failures as at all dependent on lapse of time between the first attack and the second. He held that, as in the cases of similar infectious diseases, the rule was that one attack gave absolute protection against a second, but that at the same time there was an appreciable number of exceptions to this rule, with regard both to small-pox and other infections, and he looked on small-pox after vaccination as exemplifying such exceptions. Independently of failures due to the use of spurious matter, vaccinia being essentially variola would occasionally fail to protect, just as variola itself failed, but in neither case was lessening protective power from lapse of time the cause of such failure. This view, in its application to variola, was apparently held almost universally by the medical profession. There were exceptions to the rule that one attack prevented a subsequent attack, but the rule remained all the same. If, many years after suffering from unmistakable small-pox, an individual became fevered and suffered from backache and headache which departed on the appearance of an eruption on the forehead and wrists, or over the whole body, the disease so manifesting itself was not regarded as small-pox. According to the appearance of the eruption, whether papular, vesicular, or pustular, various names were applied—horn-pock, nirle-pock, stone-pock, water-pock, chicken-pox, swine-pox. All such eruptions were customarily looked on as we look on chicken-pox at the present day, namely, as having no affinity with small-pox. If, on the contrary, a person were attacked in adult life by severe and unmistakable small-pox, and if part of his history was to the effect that in infancy or youth he had suffered from an attack, probably slight, of what had been regarded as small-pox, the verdict would be that the nature of the first attack had not been understood, that it must have been chicken-pox, or horn-pox, or one of the other varieties of such eruptive diseases. To begin with, therefore, Jenner's view as regards the protective power of variola was simply that which belonged to the time in which he lived, and his investigations into the protective power of cow-pox led him to regard it not only as small-pox of the cow but as having the same permanent protective power. In the *Inquiry* he reports cases of milkers who, having had cow-pox so long as 20 or 30 or 40 or 50 years before, had, during the whole of that period, been protected against small-pox when freely exposed to it or when purposely inoculated with it. In the present day, in explaining this lengthened duration of protection, we would attach great importance to the fact that the original operation, the accidental inoculation of the milker's hand with cow-pox, had taken place, not in infancy, but in early adult life, after childhood had passed, after growth and development had almost ceased—that it was practically equivalent to primary vaccination performed in adolescence or adult life, which itself, in its protective effect, is equivalent to revaccination; and we know, as a

matter of fact, that very few persons so protected are ever afterwards attacked by small-pox.

In this country, largely, no doubt, from Jenner's teaching, the need for revaccination was a long time in becoming recognised, and when the frequent occurrence of post-vaccinal small-pox could no longer be disputed, it was thought by many that the original stocks of lymph must have deteriorated through long removal from their bovine sources. Return to the cow was urged as the way out of the difficulty, and from about 1836 to 1841 a group of investigators—Estlin, Ceely, and Badcock in this country, and Bousquet on the Continent—sought after cow-pox, natural or artificial, the latter by variolation of cows.

By this time, however, the truth about the need for systematic revaccination had been realised in Germany, and vaccination of recruits was made compulsory in the Würtemberg army in 1833, the Prussian army in 1834, the Hanoverian army in 1837, the Baden army in 1840, and the Bavarian army in 1843. Dr. Werner, as quoted by Dr. Edwardes, states the results. In the Prussian army in the ten years preceding the order, the deaths had been as follow:—

Year.	Deaths.	Year.	Deaths.
1825	12	1830	27
1826	16	1831	108
1827	23	1832	96
1828	35	1833	108
1829	35	1834	38

The order was dated June 16, 1834, and in the next five years the deaths were 8, 9, 3, 7, and 2 respectively. Then in thirty years, 1840-69 inclusive, the total deaths were 51, the average being less than 2. Previous to 1834 there had been a higher small-pox death-rate in the army than in the civil population, but this was quickly altered, so that, while in the decade 1825-34 the deaths per 1000 in the army had been 3·6, and in the civil population 2·7, the figures in the thirty-five years 1835 to 1869 were as follows, in successive quinquennia:—

Army: 0·49, 0·21, 0·06, 0·14, 0·04, 0·12, 0·11
Population: 1·9, 2·1, 1·3, 2·6, 1·3, 3·0, 3·7

In the Würtemberg army there was not a single death from small-pox in the twenty years 1851-70, and in the Bavarian army there were only 6 deaths in the twenty-eight years 1843-70, whereas in the nine years 1828-36 there had been 52 deaths. When the small-pox pandemic swept over Europe in 1870-74 it differentiated in a very striking manner between the Prussian and Austrian armies, the former being revaccinated and the latter not. The Austrian attack-rates per 100,000 men were as follows in the eight years 1870-77 inclusive—687, 816, 1798, 1658, 1003, 386, 275, 412. The Prussian rates for the years most nearly corresponding to these were 31, 566, 684, 101, 36, 7, 8, 6.

As regards the French and German armies in 1870-71 the Royal Commission on Vaccination wrote as follows:—

A comparison of the mode in which the general small-pox epidemic of 1870-71 affected the German and French armies in those years is especially worthy of attention. In the year 1834 vaccination was made compulsory for soldiers in the Prussian army. Although it may not have been enforced with complete thoroughness, there seems to be no doubt that the German army was, on the whole, a well-vaccinated class at the time of the campaign of 1870-71. We do not think there can be any real doubt that the French army was, during the same period, in a condition in that respect less satisfactory. According to the official returns the number of small-pox deaths in the German forces during the years in question was only 316. It was stated by Monsieur de Freycinet, when Minister of War, that 23,400 French soldiers died of small-pox during the years 1870-71. We have not been able clearly to ascertain how these last figures were procured. They were not derived directly from any official return. It would seem that the average derived from a limited number of returns relating to particular portions of the army was applied to the army as a whole. It is quite possible, therefore, that the figures given may not be accurate, and that the number stated is in excess of the real number of deaths; but we do not think it is possible to doubt that the ravages of small-pox in the French army were very great, and that the mortality was enormously in excess of that suffered by the force which was opposed to them. Various facts which have been deposed to—as, for example, the small-pox deaths in the ranks of the French soldiers imprisoned in Germany—confirm this view, which receives further confirmation by a comparison of the small-pox deaths in the French and Prussian armies in the time of peace which immediately preceded the war. In 1869 there were 63 deaths from small-pox in the various French garrisons. In the four years from 1866 to 1869 there were 380 deaths from small-pox, 323 of them being in the active army. On the other hand, the total number of deaths from small-pox in the Prussian army from 1835 to 1869 was but 77.

In Germany, compulsion was extended from the army to the general population by a law dated April 8, 1874. It enacted that all children are to be vaccinated in the course of the second year of life, and that all school children are to be vaccinated in the course of the twelfth year of life unless they have had small-pox or been successfully vaccinated within the preceding five years. In Prussia, in addition, compulsory vaccination can be carried out in any house or locality where epidemic small-pox occurs. Also, as already said, recruits are revaccinated on entering the army. But in Germany, as in this country, compulsion is not absolute, and punishment of parents or guardians for failure to obey the law is by fine, or by imprisonment not exceeding three days. Germans, however, are a law-abiding people, and the amount of default is not great. The facts for 1902 abstracted from the official Reports may be given in detail, and are as follows:—*Primary Vaccination.*—The number of infants due in 1902 for primary vaccination was 1,870,895. Of these 71,784 were excused on the following grounds:—

(1) Had small-pox, 63;[1] (2) had already been vaccinated successfully in the previous year (before their compulsory vaccination was due),

[1] Most of these were in districts bordering on other countries where vaccination is not so fully carried out—Russia, France, etc.

ERRATUM

Page 791, line 1, *for* 6830 *read* 68,630

6830; (3) had been vaccinated in previous year but not inspected before the end of the year, 3091. These three groups make a total of 71,784, leaving 1,799,111 to be vaccinated. Of these there were vaccinated (1) successfully, 1,530,301; (2) unsuccessfully, 38,738; (3) with the result unknown because they had not been inspected before the end of the year, 3489. The total of these three groups is 1,572,528, and it leaves 226,327 to be accounted for. These are made up as follows:—(1) Postponed under medical certificate, 175,206; (2) gone away and not found, 17,080; (3) unlawfully in default, 34,041. Taking the last two groups as representing default in the sense in which the term is used in this country, and calculating it on the original total of 1,870,895, the percentage is 2·7. Regarding cases postponed under medical certificate, the law is that "A person, liable to vaccination, who cannot according to medical testimony be vaccinated without his life or health being endangered, must be subjected to vaccination within a year after the cessation of the cause of such danger. In cases of doubt as to whether that danger still exists, the competent official doctor's opinion is decisive without further appeal." (This official corresponds to the public vaccinator in England.) *Revaccination.*—The corresponding facts in Germany for the same year, 1902, are as follows:—There were due for revaccination 1,274,722 school children. Of these 5881 were excused, namely, (1) had small-pox within the last five years, 85;[1] (2) had been successfully vaccinated within five years, 5796. There remained 1,268,834 to be revaccinated. Of these 1,236,516 were operated on with the following result: (1) successfully, 1,162,036; (2) unsuccessfully, 72,626; (3) result unknown (not inspected), 1854. There remained not revaccinated 32,298, and these are grouped thus:—(1) Postponed under medical certificate, 17,460; (2) absent from school on the day appointed for revaccination, 6642; (3) gone away and not found, 2942; (4) unlawfully in default, 5254. It will be observed that the postponements of revaccination under medical certificate are less than a tenth of the postponements of primary vaccination. There is no reason to think that if obligatory revaccination were introduced in this country the experience would be dissimilar. The section of the Act already quoted with regard to primary postponements applies also to revaccination. If the default be regarded as including the last three groups in the above statistics, namely, 6642 + 2942 + 5254, and if this be calculated on the total of 1,274,722 due for revaccination, the percentage is 1·16. If it be assumed that the 6642 absentees were afterwards revaccinated, the default would be only 0·64 per cent.

The above are the facts as to German vaccination and revaccination under the imperial law of 1874. What are the facts as to small-pox prevalence before and after the passing of the law? For Prussia the following table gives the figures from 1816 to 1902 inclusive:—

[1] See footnote, p. 790.

MORTALITY FROM SMALL-POX IN PRUSSIA, 1816-1902 PER MILLION LIVING

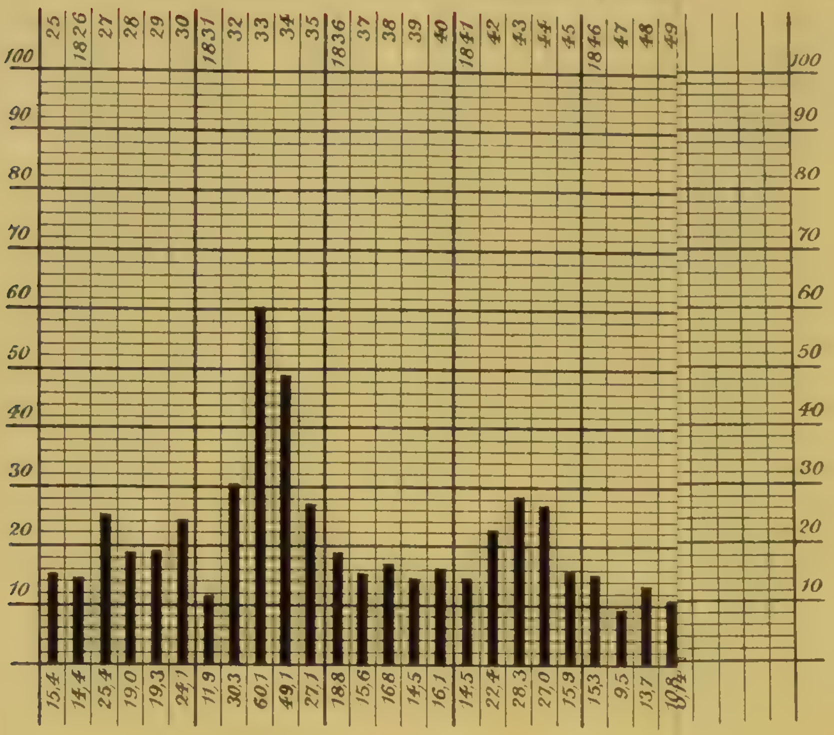
Previous to 1874						Since 1874.	
Year.	Rate.	Year.	Rate.	Year.	Rate.	Year.	Rate.
1816	453	1836	188	1856	75	1875	36
1817	278	1837	156	1857	133	1876	31
1818	295	1838	168	1858	264	1877	3
1819	208	1839	145	1859	196	1878	7
1820	106	1840	161	1860	190	1879	13
1821	170	1841	145	1861	302	1880	26
1822	205	1842	224	1862	211	1881	36
1823	199	1843	283	1863	338	1882	36
1824	145	1844	270	1864	463	1883	20
1825	154	1845	159	1865	438	1884	14
1826	144	1846	153	1866	620	1885	14
1827	254	1847	95	1867	432	1886	5
1828	190	1848	137	1868	188	1887	5
1829	193	1849	108	1869	194	1888	3
1830	241	1850	157	1870	175	1889	5
1831	119	1851	130	1871	2432	1890	1
1832	303	1852	189	1872	2624	1891	1
1833	601	1853	395	1873	357	1892	3
1834	491	1854	436	1874	95	1893	4
1835	271	1855	97			1894	3
						1895	0·8
						1896	0·2
						1897	0·2
						1898	0·4
						1899	0·8
						1900	1·4
						1901	1·4
						1902	0·3

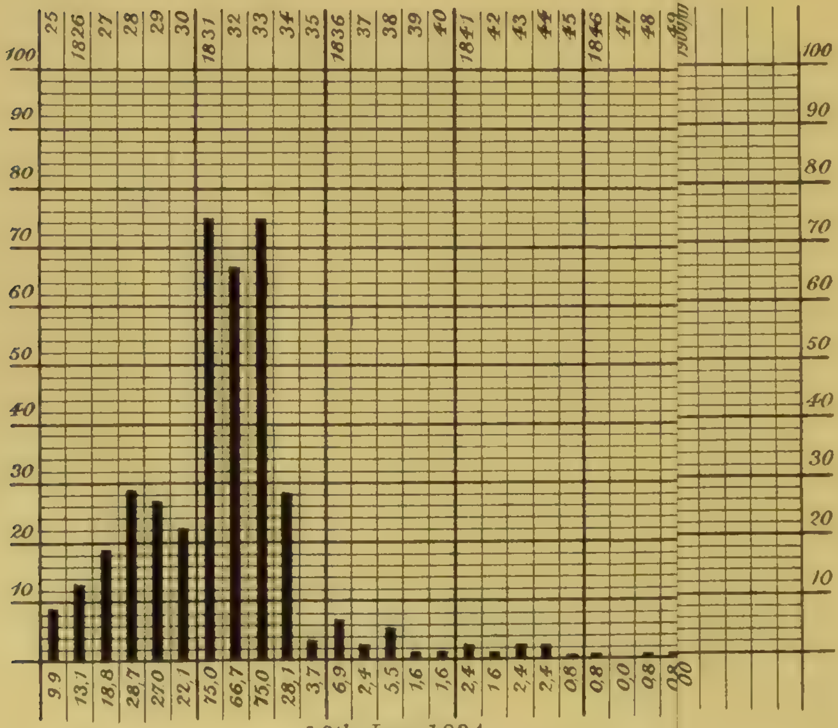
In such statistics Austria, where vaccination is not compulsory, has commonly been taken for comparison with Prussia, but since 1891 the administrative authorities have been most active in promoting vaccination, and small-pox has accordingly diminished, so that the contrast is not only between Prussia and Austria but between Austria before and since vaccination has been the subject of so much administrative effort.

Dr. Edwardes gives the following table of small-pox in Germany before and after the passing of the law :—

[TABLE

(Before 1874 *no co*





16*th June* 1834.

Vaccination and revaccination of

The figures are taken from : Contributions for ju
from the Imperial B

THE RESULTS OF THE GERMAN VACCINATION LAW, 1874

Small-pox Deaths per Million Living.

Year.	Bavaria.	Würtemberg.	German Empire.[1]
(1) Before the law of 1874—			
1866	120	133	
1867	250	63	
1868	190	19	
1869	101	74	
1870	75	293	
1871	1045	1130	
1872	611	637	
1873	176	30	
1874	47	3	
(2) Since 1874—			
1875	17	3	
1876	13	1	
1877	17	2	
1878	13	0	
1879	5	0	
1880	12	5·6	
1881	15	3·6	
1882	12	6·6	
1883	6	35·2	
1884	1	11·6	
1885	3	0	
1886	1	1	4·2
1887	1·8	0	3·5
1888	3·8	0·5	2·3
1889	5·2	0	4·1
1890	1·5	0	1·2
1891	1·2	0	1·0
1892	0·5	0	2·1
1893	0·7	1	3·1
1894	0·3	0	1·7
1895	0·2	0	0·5
1896	0·2	0	0·2
1897	0	0	0·1
1898	0·3	0	0·3
1899	...	...	0·5

Chart 14 displays both contrasts.[2] Still another contrast may be shewn diagrammatically. Compulsory revaccination began in the Prussian army so early as 1834, and in the general population not until 1874. Up to 1874, therefore, a great difference is manifest between small-pox in Prussia and in its army. But even the already revaccinated military population was benefited by extension of the practice throughout the whole country, the benefit consisting in diminished opportunity of infection of any soldiers who were still in any degree susceptible to small-pox. The chart, which gives the figures up to 1901, shews that after 1874 there were only two deaths from small-pox in the whole Prussian army, one in 1884-85 and the other in 1888-89.

[1] Statistics begin in the year 1886.

[2] From the *German Empire Vaccination Law*, Berlin, 1904. Printed by B. Paul, Berlin, S.W. 48.

Contrasting modern Germany with modern England, the following figures (from Dr. Bruce Low's Report (40)) indicate part of the price which this country pays for its folly in neglecting revaccination.

NUMBER OF RECORDED DEATHS FROM SMALL-POX IN GERMANY AND ENGLAND DURING THE TWELVE YEARS 1891 TO 1902 INCLUSIVE

Country and Date of Census.	Population.	1891.	1892.	1893.	1894.	1895.	1896.	1897.	1898.	1899.	1900.	1901.	1902.	Total in Years.
Germany (1900) . .	56,367,178	49	108	157	88	27	10	5	15	28	49	56	15[1]	607
England and Wales (1901)	32,526,075	49	431	1457	820	223	541	25	253	174	85	242	2461	6761[2]

Small-pox Isolation in Germany.—Dr. Bruce Low's report gives incidentally some remarkable evidences of the practical value of systematic revaccination. In a most valuable letter to the *Times*, Mrs. Garrett Anderson, M.D.(51), indicates the enormous expense caused by the erection and maintenance of small-pox hospitals in this country, and the loss of time, work, and money caused by small-pox epidemics. But in Germany small-pox and small-pox hospitals are alike almost non-existent. For London, with its population of five millions, 2500 beds have to be reserved in hospitals far removed from the city, whilst for Berlin, with its two millions of population, 12 beds in a pavilion of a general hospital within the city are sufficient. Other towns have more or less similar arrangements. In Wiesbaden (estimated population 92,301) there is, in the general hospital of 300 beds, a wooden pavilion of 16 beds which is regarded as giving accommodation for small-pox; but there had been no small-pox in Wiesbaden for eleven years, and the beds were being used for non-infectious cases. In Munich (estimated population 544,714) there is a hospital of 1320 beds near the centre of the city, and a pavilion containing 14 beds is used for small-pox, and occasionally for "contacts." In Nuremberg (estimated population 294,819) the general hospital has 946 beds, of which 12 are for small-pox; but, as in Wiesbaden, there had been no one to occupy them for eleven years. In Dresden (estimated population 518,405) the Friedrichstadt Hospital has 1058 beds, of which 20 are for small-pox; and Professor Schmidt told Dr. Bruce Low about "the procedure which would be followed if a case of small-pox were admitted," but none had been brought during his term of office, and there had been no small-pox deaths in Dresden for ten years. In Stuttgart (estimated population 191,645) the Katharine Hospital has 700 medical and surgical beds, and devotes to small-pox a *Ducker* hut of 6 beds; but there had been no small-pox for six years, and the hut was out of repair. The case six years before was that of a Russian. Generally, small-pox pavilions are in no way shut off from the rest of the establishment; food is supplied

[1] The number of small-pox deaths for 1902 has been supplied to Dr. Bruce Low from the Central Imperial Health Office at Berlin, subject to any slight corrections which may be found necessary when the medical statistics for 1902 are issued officially.

[2] There were 754 deaths from small-pox in England and Wales during 1903, but Dr. Bruce Low has been unable to obtain the corresponding figures for Germany for that year.

from the central kitchen, and soiled linen, after steeping in a disinfecting solution, is sent to the general laundry. Small-pox nurses and attendants are at once revaccinated, but for the rest of the hospital reliance is placed on statutory vaccination and revaccination. Regarding such small-pox as does occur in Germany, Dr. Low writes: "There appeared a general consensus of opinion that a considerable proportion of the small-pox cases now met with in Germany were in the persons of foreigners, especially Russians, Austrians, and Italians, many of whom come to Germany to work in new industrial undertakings or as labourers on the construction of railways or other public works. Many of the outbreaks of small-pox reported in Germany occur in towns and districts situated on or near the Russian or Austrian frontiers, especially the former. There are considerable commercial communications between some large towns in Germany and Russia, and small-pox has been observed in Russian commercial men visiting Berlin and other places in connexion with their business. Further, Russian and other emigrants passing through Germany on their way to Hamburg or other ports, by rail, have been known to infect persons whose duties, as railway officials, for example, caused them to visit the trains, or who otherwise came casually into contact with these travellers." Here is an illustration of how foreigners may be infected in Germany. Professor Weintraud of Wiesbaden told Dr. Bruce Low how "while resident medical officer some years ago at the Berlin Charité Hospital two small-pox cases were admitted for isolation. As there had been no opportunity for demonstrating the clinical characters of small-pox for some time, he was deputed by the chief physician to give instruction on the diagnosis of small-pox to some 260 students, in detachments, by the bedside of these two patients. As vaccination and revaccination are compulsory in Germany, it was not thought necessary to make inquiries as to this matter. But at the end of twelve days 2 students out of the 260 fell ill with the initial symptoms of small-pox, and each passed through an attack of the disease. Both were Italians who had not been revaccinated."

British Army.—In our own country there is, unfortunately, no such systematic national revaccination and no such immunity from small-pox as in Germany. In the army and navy, however, systematic revaccination of recruits is practised, but the proportion of failures of the operation is large, and no exact information is published as to the actual percentage ultimately revaccinated with success. Yet the figures are sufficiently striking, as given by the Royal Commission in sections 331-339 of their Final Report. The Army Revaccination Order dates from 1858, and as the men previously recruited passed out of the force the influence of the new system became manifest, so that the attacks per 10,000 of the strength, which in the home force had ranged from 12 to 41 in the years 1847-58, amounted only to 20 in the whole 14 years 1881-94, with which last-mentioned year the table ends. In the force in the Colonies the attacks per 10,000 of strength averaged only fractionally more than one per annum in the same 14 years, and there was not a single death. In India

and Egypt, where opportunities of infection are much more numerous, the figures are higher, especially in Egypt in 1887-89.

Regarding the Sheffield epidemic, the Royal Commission says :—

The average strength of the troops stationed at Sheffield during 1887-88 was about 830 of all ranks. The whole of these were, or should, in accordance with the army regulations, have been at one time revaccinated, or vaccinated in the exceptional cases where they had not been previously vaccinated. Twelve men, or 1·4 per cent of the total strength, contracted small-pox, and of these one died. Not one of the soldiers who had contracted small-pox had been successfully revaccinated. During the period of the epidemic the men mingled freely with their friends in the town, and although the neighbourhood of the barracks was one of the first localities invaded by the disease, no successfully revaccinated soldier quartered in Sheffield suffered from small-pox.

As already indicated, there seems distinct room for improvement in army revaccination arrangements.

British Navy.—Vaccination of recruits in the Navy has been practised since 1864, and in 1871 an order for the vaccination of the whole force was issued, but there was no regulation as to natives joining abroad, nor as to "foreigners," until 1873, when an order was issued for their vaccination on enlistment. The following table shews how small-pox has diminished in the Navy, wherever stationed. The figures up to 1894 are from the Royal Commission's Report, and those for later years have been kindly supplied to me by the Director-General of the Medical Department of the Navy.

Year.	Attacks of Small-pox to every 10,000 of the Force.	Deaths from Small-pox to every 10,000 of the Force.	Year.	Attacks of Small-pox to every 10,000 of the Force.	Deaths from Small-pox to every 10,000 of the Force.
1860	51	3·9	1883	2	0
1861	50	3·8	1884	1	0
1862	17	3·1	1885	1	0
1863	22	2·8	1886	2	·6
1864	87	6·2	1887	·2	0
1865	32	2·9	1888	4	·2
1866	48	1·6	1889	1	·2
1867	49	2·7	1890	1	·4
1868	16	·4	1891	3	0
1869	17	1·0	1892	2	·3
1870	9	·2	1893	1	0
1871	31	2·5	1894	3	0
1872	19	2·3	1895	1·7	0
1873	3	·2	1896	1·5	·2
1874	2	·2	1897	6·3	·2
1875	4	·2	1898	2·8	·2
1876	5	1·3	1899	1·6	·2
1877	4	0	1900	1·3	·1
1878	2	0	1901	·9	·1
1879	12	3·1	1902	1·4	·2
1880	2	·2	1903	·2	0
1881	6	·7	1904	1	0
1882	2	·5			

The facts regarding the *Postal Service* furnish another illustration of the value of revaccination. In 1883, Sir Charles Dilke said in the House of Commons:—"In the case of persons permanently employed in the postal service in London, averaging 10,504, who are required to undergo vaccination on admission, unless it has been performed within seven years, there has not been a single death from small-pox between 1870 and 1880, which period included the small-pox epidemic, and there have been only 10 slight cases of the disease. In the telegraphic department, where there is not so complete an enforcement of vaccination, there have been only 12 cases in a staff averaging 1500 men."

The Royal Commission gave the following additional statistics:—

Year.	General Post Office.		
	Number of Established Officers Employed.	Number of Cases of Small-pox.	Number of Deaths from Small-pox.
1891	47,264	None	None
1892	54,198	2	None
1893	58,311	4	None
1894	60,490	11	1

Small-pox was prevalent in London in the period included in this table, and the Commission add: "It is noteworthy that, in the year 1892, 12 officers were absent from duty on account of the presence of small-pox in their houses; in 1893, 44; and in 1894 as many as 53." In Sheffield, at the time of its epidemic, there were 290 persons on the permanent staff of the Post Office, and the regulations required revaccination before engagement: none were attacked by small-pox, though much exposed to it in the course of their duties as letter-carriers, telegraph boys, etc.

The Glasgow Epidemic of 1901-2.—The City of Glasgow afforded in its small-pox epidemic of 1901-2 an exceptionally valuable field for observing the influence of revaccination. The working-class population of Glasgow lives in huge tenement buildings, usually four storeys in height, with multiple dwellings on each flat, all entering from common passages and stairways. Opportunities for infection, therefore, are specially great. Belvidere Hospital, where Glasgow small-pox was treated, is situated at the east end of the city, and, as often occurs in such circumstances, in the east-end population there was quite exceptional prevalence of small-pox. In these circumstances the Corporation offered systematic revaccination throughout the whole community over five years old. The total population over that age was estimated at 675,887, and the total cases of small-pox from the beginning of 1901 to May 1902 were 1858. The following table shews the progress both of vaccination and small-pox in this population fortnight by fortnight, those who accepted the Corporation's offer being distinguished from those who did

not. The progress of revaccination is indicated by the figures, and the gradual extension of the practice until it had embraced over 400,000 persons is well seen in the table, along with the corresponding diminution in the numbers who neglected the protection offered them. From beginning to end it will be observed that small-pox absolutely confined itself to those who did not submit to the operation. Not a single recently revaccinated individual was attacked by the disease from beginning to end of the period. There being most small-pox in the east end, vaccination was most resorted to there.

Not Recently Revaccinated and Recently Revaccinated Population of Glasgow, over five years of age, in each Fortnight, with the cases of Small-pox occurring in each Class. (Dr. A. K. Chalmers.)

	Not Recently Revaccinated.		Recently Revaccinated.	
	Population.	Cases Registered.[1]	Population.	Cases Registered.
January 12, 1901 .	675,887	23	0	0
,, 26 . .	674,816	350	1,071	0
February 9 . .	671,025	202	4,862	0
,, 23 . .	634,213	127	41,674	0
March 9 . .	556,561	299	119,326	0
,, 23 . .	518,426	161	157,461	0
April 6 . .	474,694	92	201,193	0
,, 20 . .	429,056	67	246,831	0
May 4 . .	384,371	28	291,516	0
,, 18 . .	366,125	18	309,762	0
June 1 . .	352,633	11	323,254	0
,, 15 . .	347,777	2	328,110	0
,, 29 . .	345,293	8	330,594	0
July 13 . .	281,867	1	394,020	0
November 16 . .	279,452	1	396,435	0
,, 30 . .	279,232	5	396,655	0
December 14 . .	279,020	4	396,867	0
,, 28 . .	278,796	0	397,091	0
January 11, 1902 .	278,623	28	397,264	0
,, 25 . .	278,152	23	397,735	0
February 8 . .	277,653	23	398,234	0
,, 22 . .	277,134	147	398,753	0
March 8 . .	276,033	92	399,854	0
,, 22 . .	274,611	85	401,276	0
April 5 . .	272,694	36	403,193	0
,, 19 . .	271,619	15	404,268	0
May 3 . .	271,032	10	404,855	0

The communities living in these great four-storied buildings were sharply differentiated by acceptances and refusal of vaccination, whilst the differentiation made by small-pox was equally sharp and equally

[1] The cases under five years have not been excluded from these figures, because their allocation through the various fortnights would have been difficult, and their inclusion is unimportant. In the 1900-1901 part of the outbreak these numbered 60, 54 of whom (including 30 cases occurring under one year) were unvaccinated primarily.

definite. The two differentiations coincided from beginning to end. The disease passed by the recently vaccinated and found all its victims among the unprotected population. It went from door to door like a rate collector taking his dues only from those who had not accepted the offered relief.

Small-pox Hospital Nurses.—While this Glasgow population was, owing to its housing arrangements, exceptionally exposed to small-pox, there occur every now and then conditions which furnish even a severer test. No opportunities for infection are comparable with those of the staff of small-pox hospitals. The nurses live in a constant atmosphere of infection. Their duties with regard to nursing and cleansing of patients, dressing of facial eruptions, removing of soiled bedding, and other such routine work, subject them to unequalled risks of infection. The statistics with regard to their resistance to attack by the disease are now well known, and some of them will be noted here.

At Homerton Hospital, in 1871-1877, 366 persons were employed. All but one was revaccinated, and she was the only one who took small-pox. In the small-pox hospital-ships of the Metropolitan Asylums Board in the twelve years 1884-1895, the number of attendants varied from below 50 to upwards of 300, and in only three of the twelve years were there any cases of small-pox. The total cases in the twelve years were 12. In one of the 12 the disease appeared within three days of her entering the hospital, in another within nine days, in 4 others within ten days, and in 4 others within twelve to fifteen days. The Commission state that "none of the recorded cases appear to have been revaccinated successfully prior to the period of incubation of the small-pox, though the operation was in all cases attempted shortly after joining." During the London epidemic of 1901-2 the small-pox staff of the Asylums Board consisted of 974 persons, 494 of these being nurses. Only 2 took small-pox, and 1 of these had not been revaccinated because she had had small-pox previously. In the Highgate Small-pox Hospital during sixty years, beginning 1836, the only member of the staff attacked by small-pox was a gardener. Of 137 nurses and attendants since May 1883, 30 had had small-pox previous to entering the service. All the others were revaccinated with one exception, and he was the gardener who took the disease.

In the Sheffield hospitals in the year ending 31st March 1888 there were 1798 cases of small-pox. There were 161 attendants, etc., of whom 18 had had small-pox previously and escaped attack, 63 had been vaccinated in infancy, and 6 of these were attacked and 1 died. The other 80 were successfully revaccinated, and all escaped the disease.

In Leicester in 1892-93, owing no doubt to the popularity of anti-vaccination, some of the nurses refused vaccination. The staff consisted of 40 persons, of whom 14 had had small-pox or been revaccinated before the small-pox outbreak, and 20 were revaccinated at the time. Among these 34 one mild case occurred in a nurse who had been revaccinated ten years previously. Six of the nurses refused revaccination,

and 5 of these took the disease, one of the attacks being fatal. The sixth who escaped was the matron, who had less intimate relation to the nursing of the patients. Small-pox returned to Leicester in 1903-4, but there was by that time no material for an exactly similar control experiment. The resident staff was 74. All excepting 3, who had already had small-pox, had been recently vaccinated, and all escaped the disease. Yet the hospital did furnish a control experiment. Two workmen temporarily employed at it were not revaccinated, and both took small-pox, though they were never in the wards. The medical officer brought into the wards his own vaccinated children and had them photographed at the bedside of a small-pox patient.

In Glasgow 230 workmen were employed at Belvidere in 1903 extending the small-pox hospital accommodation. Of these, 217 were successfully revaccinated, and 13 refused or were passed over. Not one of the 217 took small-pox, but 5 of the 13 were attacked and 1 died.

Still another control experiment as regards the infectivity of small-pox and the power of vaccination to resist it is to be found where, as occasionally happens, a mother with a baby at the breast has to be admitted to hospital, and where there is no one at home to nurse the child. In Stirlingshire recently I had experience of two such cases. The infants were vaccinated before admission. They lived and were nursed in the small-pox ward and came away unharmed. Similarly in the recent Dewsbury epidemic Dr. Maynard Ashcroft writes that "there was a considerable number of children and infants, who, though not themselves suffering from the disease, were admitted to the hospital because the houses they lived in had to be closed owing to the parents being stricken with small-pox, or because the mother could not leave the infant at home; these children were efficiently vaccinated, and never in any single case did they shew the slightest trace of small-pox, and yet they were daily in contact with and living amongst persons suffering from the disease, often in its most severe forms and in all stages."

It has been suggested that the remarkable immunity of small-pox nurses to infection is due to their being in some way accustomed to or seasoned against the disease, but that cannot be alleged regarding the children, and there is no meaning in such a statement with reference to the nurses. They are not in any way seasoned against small-pox when they first begin to nurse it. The Leicester nurses who refused vaccination were duly attacked by small-pox, and the other exceptions that from time to time occur are almost invariably illustrations of the fact that if revaccination is neglected there is no immunity from seizure.

At Salford, during the epidemic of 1903, Mr. Mullen, the medical superintendent, reports that "with very few exceptions all the nursing staff of the Ladywell Sanatorium, all of whom were successfully revaccinated, were afforded the opportunity of adding to their experience by being detailed in turn for attendance on small-pox patients. Not one of the staff contracted the disease."

The same experience may be illustrated otherwise. If the nurses

belong to a hardened class rendered indifferent by custom, and if that condition affords them protection it should protect them similarly with regard to other infectious diseases; but regarding Homerton Hospital, Dr. Collie, the late medical superintendent, stated that "the only way in which nurses become seasoned against fever is by taking the disease."

Sir Richard Thorne in his evidence before the Royal Commission pointed out that when typhus was in Newcastle in 1882 only 5 of 14 nurses escaped attack, and that of the attacked 2 died. In Gateshead the experience was even more striking, the medical officer writing that "every nurse who has been more than a fortnight in the typhus wards has suffered from typhus." In the ten years ending 1881, in the Homerton, Stockwell, and Liverpool Road Fever Hospitals, 133 of the staff were attacked by various fevers, and 25 died. The Royal Commission state that in the Asylums Board Hospitals in 1887-95 as many as 704 of attendants suffered from scarlet fever, diphtheria, or enteric fever.

The evidence of the protective value of vaccination as furnished by the experience of the staff of small-pox hospitals is stronger than is perhaps to be found with regard to any other subject in the whole domain of medicine, and indeed it is infinitely stronger than that on which conclusions are based in almost every other department of science and of everyday life.

Small-pox after Revaccination.—It will be observed that the most striking evidence of the power of revaccination is to be found in the protection of the administrative staff of small-pox hospitals, and of children admitted for convenience to such hospitals because their guardians are interned there, and of the 400,000 inhabitants of Glasgow who accepted vaccination in presence of an epidemic. The fact common to nearly all these examples is the recency of the protective operation. Nurses are seldom allowed to go more than ten years without its repetition, especially in the presence of an epidemic. The protective power of revaccination is not in all cases absolutely permanent. It may safely be regarded as of longer duration than that of infantile vaccination, because revaccination is done on a body in which growth is approaching completion, and tissue-change is lessening, whereas infantile vaccination is performed on a being only a stone or two in weight, and the protection will become diluted and diminished in value as development proceeds towards manhood. No doubt in Germany a fraction of the population is susceptible to small-pox infection, but the vaccinal condition of the empire as a whole is such that small-pox can hardly ever find a footing. The susceptible are surrounded by a cordon of millions of insusceptible people, and infection cannot reach them. The disease appears from time to time near the borders, where there is constant intercourse with less vaccinated countries—Russia, Austria, and France—but so introduced, it fails to invade Germany. It dies out like fire applied to damp grass. So it is with regard, say, to our own army. As already noted, revaccination of soldiers appears not to be carried out so thoroughly as it might be, but the forces in this country have less opportunity of infection than in India

or Egypt, and it is these places that probe the weak spots in the system of military vaccination. Any one in this country who is likely to be exposed to the infection of epidemic small-pox, whether as medical attendant or otherwise, should not hesitate to renew his protection if his revaccination is many years old or had produced a much modified local result when performed.

Sanitation and Small-pox.—It is continually suggested by opponents of vaccination that the diminution of small-pox prevalence is due to sanitation. But the meaning attached to the term "sanitation" varies with circumstances. In its broadest sense it includes all practicable and available means for conserving the public health, such as vaccination and isolation, but its use is often conveniently limited so as to refer only to measures for improving the surroundings of the individual, by providing him with pure air, water, and food, good house accommodation, and so forth. These agencies improve the general health, and are in their degree good against all human diseases, whether local or general, infectious or non-infectious; and as regards small-pox, lessening of overcrowding and a freer supply of better air are of much more consequence than the rest. But pure water-supply, which causes diminution in the prevalence of enteric fever, has no similar effect with regard to small-pox, and Jennerian vaccination does not prevent enteric fever. So also milk, which can convey scarlet fever, cannot carry whooping-cough or measles; so that the guarding of the milk-supply does not diminish these diseases. Sanitation embraces all such measures, but they are of particular rather than general application, and the one sanitary measure which really prevents the spread of small-pox is vaccination, just as a safe water-supply is the preventive of spread of cholera. Excluding vaccination, all the rest of sanitation cannot account for the facts of experience already set forth in this article.

As already stated, one striking feature in the case for vaccination consists in the convergence of all lines of evidence towards the one conclusion. This test was applied to the proposition that sanitation is the cause of the decline in small-pox in a pamphlet prepared for the Council of the British Medical Association, as follows:—

Whooping-cough and measles deaths still belong to childhood as in the last [18th] century, while small-pox deaths have been removed from childhood to later periods of life. How could sanitation account for this differentiation? If it be suggested that because sanitation confers a special benefit on children it may have altered the age-incidence of small-pox, the answer is got by looking at facts. In Germany, as we have seen, vaccination is not compulsory till the second year, and over 40 per cent of all the small-pox deaths occur under two years of age. In Scotland the vaccination age is six months, and children under six months make just about the same contribution (138 deaths per 1000 deaths) to the total small-pox deaths as they did (139 deaths per 1000) before the vaccination law was passed. But in the next half-year of life—the half-year of vaccination—the contribution has fallen from 153 to 47. Surely this is vaccination and not sanitation. In a community attacked by small-pox, how could

sanitation at home protect postmen going from door to door day after day in infected districts? In Leicester, how could sanitation account for the revaccinated nurses escaping small-pox and the nurses who had refused revaccination taking small-pox? How could sanitation cause small-pox to pass over vaccinated children and seize on unvaccinated children in houses invaded by small-pox in Dewsbury, Leicester, and Gloucester? How can sanitation have caused the fatality of small-pox cases to be much less among the vaccinated than among the unvaccinated in these towns, especially if vaccination weakens the system, and makes it less resistant to disease, as is alleged by anti-vaccinationists? How could sanitation cause children with three or four vaccination marks to have a less fatality from small-pox than children with one or two vaccination marks? In Glasgow, while sanitation was going from bad to worse in the early part of the [19th] century, vaccination was introduced and small-pox underwent an enormous diminution, though hospitals and isolation and disinfection were entirely out of the question. In Gloucester, vaccination had been neglected, and in 1891 the Secretary to the Anti-Vaccination League declared to the Royal Commission that Gloucester was a very clean town, and had always been well abreast of sanitary improvements, and that its death-rate was very low. The Board of Guardians also wrote to the Commission on the same lines. But small-pox came, and the town suffered from a terrible epidemic, and ever since then the anti-vaccinationists have been declaring that there was a great want of sanitation in Gloucester. What was wanting was vaccination.

For convenience the Registrar-General many years ago grouped together places whose death-rate was low, and classified them as "healthy districts." They were nearly all found to be sparsely populated rural districts, where, though houses may be damp and overcrowded, and other insanitary conditions prevail, there is little opportunity for infection. In such places, in spite of bad sanitation, there is a lower death-rate than in towns, because, independently of sanitary effort, the atmosphere is purer. Also there is less small-pox, and it comes at a later average age, because there is less facility for spread of infection on account of the smallness of the population and the distance of house from house and village from village. In such circumstances, though there is little sanitary effort, there is little small-pox, and unvaccinated persons have a better chance of escaping small-pox attack than they have in large towns where sanitary arrangements are more elaborate.

The Control of Small-pox in Britain

I have now, as I believe, proved that vaccination can prevent small-pox, and that, in fact, it is responsible for the remarkable diminution in the prevalence of the disease now as compared with pre-vaccination times. In view of the attitude of the legislature in this country towards the whole subject of vaccination and revaccination, a very important practical question remains, namely, how we can best deal with small-pox in a country where primary vaccination is to a great extent optional, and where revaccination is, except in certain public services, entirely optional.

It was my purpose to proceed to discussion of this very important subject, including consideration of the value of hospital isolation of

small-pox, the size and situation of such hospitals, their influence on surrounding populations, their management with the view to minimising their evil influence, the value of vaccination after exposure to small-pox, observation of "contacts," the influence of epidemic type on spread of infection, and the experiences of Leicester, Gloucester, and Dewsbury with regard to vaccination and small-pox. But space does not permit this to be done in the present article, and what I have to say on these matters must be reserved for another occasion.

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FOOT-AND-MOUTH DISEASE

By Sir JOHN M'FADYEAN, M.B.

SYNONYM—*Epizootic stomatitis*

FOOT-AND-MOUTH disease is an acute febrile affection characterised by the formation of a vesicular eruption, the most constant seats of which are the buccal mucous membrane and the skin of the digits. It is highly contagious among ruminant animals, wild and domestic, and among pigs. It is frequently transmitted from these animals to human beings, and occasionally also to horses, dogs, cats, and fowls.

History.—Although there is good reason to believe that foot-and-mouth disease was unknown in this country before the last century, it appears to have prevailed at intervals in the epizootic form in Eastern Europe for centuries before its introduction into Great Britain. In the sixteenth century it was described by the Italian writers Fracastori, Ruini, and Francisi; and in 1686 and 1687 it spread over Germany and France. In the following century it appears to have had a wide distribution over the continent of Europe, and numerous epizootic outbreaks of it are recorded. In the early part of the last century it was equally prevalent in Eastern and Middle Europe, but it was not till 1839 that the disease obtained a footing in Great Britain. The precise circumstances of its introduction here are not known, but during that year it speedily acquired epizootic dimensions among British cattle. The earliest reference to it in veterinary literature is found in the *Veterinarian* for 1839, where, under the heading, "The present Epidemic among Cattle," Mr. Hill, a veterinary surgeon of Islington Green, described an outbreak in a dairy of 700 cows. Six of the cows were suddenly attacked "with a singular disease, the symptoms of which were precisely the same in each. The lining membrane of the whole of the mouth was in a state of inflammation and vesication. The tongue was involved, but the most extensive and annoying vesication was between the under lip and the gums. In two of the six it extended over the muzzle to the nostrils . . . and peculiar symptoms accompanied this—a continual catching up and shaking of one or other of the hind legs." These symptoms were at first attributed to some poisonous herbage; but that the disease was epizootic was soon made manifest, for in the course of about ten days more than 500 of the cows had been attacked.

Succeeding numbers of the *Veterinarian* contain other reports regarding the "Epidemic," the contagious character of which was soon recognised, although the possibility of its originating under "atmospheric agency" was entertained by many veterinary surgeons. Indeed, as late as 1857, Professor Simonds denied that foot-and-mouth disease was imported; and for many years afterwards this opinion was used to

combat the efforts of those who held that the disease never originated spontaneously, and ought to be opposed by measures calculated to stamp it out.

From the period of its introduction till 1866 foot-and-mouth disease was never absent from Great Britain; but by the end of the latter year, apparently owing to the operation of the measures directed against cattle plague, this country was nearly free from the disease. The next few years, however, saw an alarming recrudescence of the plague; and in 1870 and 1871 over a million animals were reported to have been attacked by it. The Contagious Diseases (Animals) Act came into force in 1878, and the repressive measures which it introduced had almost eradicated foot-and-mouth disease by the end of the following year. Unfortunately, during 1880 it began again to spread; and in 1883 nearly half a million animals were reported to have been attacked. After that date it gradually declined, until in 1886 only one outbreak was reported. For the following six years the British Islands were free from foot-and-mouth disease; but in February 1892 the disease was discovered among some Danish oxen in the Metropolitan Cattle Market. Notwithstanding the utmost vigilance of the Board of Agriculture this proved the starting-point of an epizootic during which, in England and Scotland, 5267 animals were attacked. Rigorous isolation, supplemented in some cases by slaughter of the affected animals and of those that had been exposed to the contagion, had the effect of exterminating the disease by June 1892.

Since 1892 the importation of live cattle from countries in which foot-and-mouth disease exists has been prohibited; but, nevertheless, since that date the country has thrice been invaded by the disease. On the first of these occasions the disease appeared on January 1, 1893 in a London cow-house, and six weeks later on a farm near Hastings. The London outbreak was suppressed by the prompt slaughter of all the cattle on the premises; and in the Hastings outbreak strict isolation sufficed to prevent the spread of the disease. The next visitation occurred in 1894, but it was limited to three outbreaks, in which 268 animals were attacked. The last visitation began in January 1900, and terminated in April 1901; it comprised 33 outbreaks, in which 935 animals were attacked.

In none of these recent visitations was the source of the disease traced, though there can hardly be any doubt that the contagium was in some manner brought from the Continent, on which the disease then existed at various points opposite Great Britain. None of the circumstances brought to light by the inquiries instituted by the Board of Agriculture made it appear probable that the virus had been introduced in imported straw, hay, or hides, or adhering to the clothes or persons of human beings, and, on the other hand, it is scarcely conceivable that the contagium can have been carried across the North Sea in the air. In this connexion it is a noteworthy circumstance that, in spite of the suspension of cattle traffic, the disease has on several occasions broken out in Denmark when it prevailed in Germany, and Bang of Copenhagen has suggested as a

possibility that the virus may have been introduced adhering to the feet of wild-fowl.

Etiology.—Foot-and-mouth disease is an eminently infectious malady, and its history indicates that it belongs to the class of infectious diseases as opposed to the miasmatic. In other words, the germ or virus of foot-and-mouth disease does not propagate itself save in the bodies of affected animals; every case of the disease is ascribable to germs derived from an antecedent case. In the vast majority of cases searching inquiry suffices to bring the source of the contagion to light; and the exceptions to this rule in no way compel us to admit that the disease is ever due to spontaneous development or miasmatic poison; since it is known that the virus of the disease possesses considerable vitality outside the body, and, adhering to inanimate objects, may be carried long distances in an active condition. Fresh outbreaks, without actual contact between animal and animal, may thus be brought about by such means as farm-yard manure, straw, hay, railway waggons, steamboats, human clothing, and so forth. Many instances have been observed in which the clothes of milkmaids or other farm-servants have transported the virus of the disease from one locality to another. It is probable also that wild animals, such as rooks, hares, and rabbits, although not themselves affected, may transport saliva of infected animals from one field to another, and thus spread the disease.

During that stage of the disease included between the rise of temperature and the appearance of the characteristic lesions the virus circulates in the blood, but after the development of the eruption the blood is no longer infective (Löffler and Frosch). On the other hand, the agent of infection appears to be always abundantly present in the fluid of the vesicles which form in the mucous membranes or skin, and in the discharge from the ulcers left by those vesicles when they burst. The buccal saliva is highly charged with the virus from the first appearance of the eruption in the mouth; but there is no reason to believe that the agents of infection are excreted by the salivary glands. In like manner the milk is probably not infective except when soiled with the contents of vesicles that have formed on the exterior of the teats or in the interior of the gland, or by the hand of the milkmaid.

To what extent the virus may be carried by the air is unknown. The older writers on the subject regarded the virus of foot-and-mouth disease as belonging to the class of *fluid contagia*, and many believed that it could be carried for miles in the atmosphere. For example, the rapid spread of the disease over nearly the whole continent of Europe in 1839, and even across the sea to England, was regarded by Haubner as conclusive evidence of the fluid nature of the virus; and it was asserted that the disease on that occasion broke out in the most isolated localities, such as mountain districts and forests, where there was no cattle-traffic with the surrounding country. At the present day it is not necessary to combat the hypothesis that the virus of foot-and-mouth disease is gaseous in its nature; and experience has proved that rigorous isolation of

infected animals is nearly always effectual in preventing the spread of the disease. In the cases which appear to constitute exceptions to this rule, it is more probable that the contagium has been carried by some undetected intermediate agent (human beings, dogs, birds, hares, rabbits, etc.) than that it was air-borne.

In illustration of the ease with which the infection of this disease may be spread by intermediary bearers, the following case may be quoted :—Gensert, a German veterinary surgeon, visited a byre in which foot-and-mouth disease existed, and remained in it for about ten minutes. Two hours afterwards, having changed his hat and coat, and washed his hands with soap and water, he started to make another visit, and drove for an hour and a half in an open conveyance. Having arrived at his destination he performed an operation on the eye of a cow. Eight days afterwards the cow shewed symptoms of foot-and-mouth disease, and within a few days all the other cattle on the premises were affected. This was the first outbreak in the neighbourhood, and Gensert, therefore, had no doubt that he had carried the contagium on his clothes.

In the preceding paragraphs the terms virus and contagium have been used to designate the causal agent of foot-and-mouth disease, but the exact nature and form of this agent are still matters of dispute.

Bacteriology.—Klein, Schottelius, Behla, Kurth, and others have at different times described bacteria or other microscopic organisms which they found in the lesions or in the blood of affected animals, and which they held to be the cause of the disease. All such claims, however, have been definitely set at rest by the researches of Löffler and Frosch, who in 1898, discovered that the fluid taken from a foot-and-mouth disease vesicle, when largely diluted with water and passed through a Berkefeld filter, still retains its virulence. The filtrate thus obtained is free from visible particles under the highest powers of the microscope, and the cause of foot-and-mouth disease therefore belongs to the class of so-called "ultra-visible viruses" (*vide* p. 168). Like all the other viruses of the same kind at present known, it is not only invisible but also uncultivable by any artificial means hitherto employed.

Pathological Anatomy.—The characteristic lesion of foot-and-mouth disease is a vesicular eruption ; and, as the name expresses, the feet and the mouth are the main seats of election of the eruption. In milch cows vesicles not infrequently form on the skin of the teats and udder ; and occasionally the eruption appears in other situations, such as the muzzle, the nostrils, the skin of the vulva and perineum, or the mucous membrane of the throat, gullet, stomachs, or intestines. The localisation of the lesions in the mouth or feet is in no way ascribable to the method of infection, though this has been asserted by some authors. Animals infected by way of the alimentary canal may have an eruption on the feet as well as in the mouth ; and an eruption in both of these situations may follow infection by inoculation at any part of the body.

In the mouth the vesicles may form on any part of the mucous

membrane; but they occur most frequently on the inside of the lips, the pad of the upper jaw, and the tongue. Their appearance in these situations is no doubt preceded by a stage of inflammatory hyperæmia, but this is seldom noticeable owing to the thickness of the epithelium. The stage of vesiculation is determined by the escape of a thin serous exudate from the vessels of the inflamed corium, and its accumulation in the deeper layers of the epithelium. Small cavities containing a clear liquid are thus formed in the rete Malpighii, and these gradually increase in size and become confluent, while the stratum corneum is stretched and upheaved into a blister-like elevation. The bursting of the vesicle is hastened by the movements of the tongue or lip, and the vesicle becomes converted into a shallow erosion or ulcer, the bright red floor of which is formed by the congested papillæ of the mucosa. The vesicles vary in size from a sixpence to a five-shilling piece, and their outline may be circular, oval, or irregular. In uncomplicated cases regeneration of the lost epithelium promptly sets in, but this is always retarded by the movements of the tongue and lips, and by the presence of adventitious organisms in the mouth.

In other situations the histology of the lesions is essentially the same as that of the buccal eruption. In the feet also the access of other microbes tends to aggravate the inflammation, which may extend to the whole vascular corium and lead to complete detachment of the hoof.

The first **symptoms** generally appear from one to eight days after infection. In cattle these are slight dulness, shivering, loss of appetite, "staring of the coat," and stiffness in movement. If taken at the time the temperature will be found to be already two or three degrees above the normal. Within a few hours these premonitory symptoms of illness are followed by others which are characteristic of the disease. The animal ceases to feed, and is reluctant to move; from time to time it makes a peculiar smacking noise with its lips, from which a more or less frothy saliva escapes. If the mouth be opened, white blister-like elevations will now be found on some part of the buccal mucous membrane; these soon burst and become converted into shallow erosions. When made to move, the animal is obviously lame or "tender on its feet"; and while standing it frequently shifts the weight from one leg to the other, and shakes its feet as if to get rid of something adhering to them. This tenderness of the feet is well marked even before the formation of vesicles; but these soon appear on the interdigital skin, or on the posterior aspect of the hoof immediately above the horn.

When the buccal vesicles have burst, the animal suffers increased pain in the mouth, rumination ceases entirely, and all food is for a time refused; in consequence of reflex irritation there is a copious secretion of saliva, much of which, from the pain of deglutition, is allowed to trickle from the mouth. The general appearance of the animal is now indicative of great depression—the eyes are dull, the ears drooping, the back arched, and the hair erect and lustreless. The bowels are generally

more or less constipated, and in milch cows the secretion of milk is greatly diminished or almost arrested.

These symptoms in moderate cases last with little or no amelioration for nearly a week, during which time the animal rapidly loses condition. At the end of that time the fever begins to subside, and the pangs of hunger compel it to attempt mastication if succulent grass or other soft food is to be had. The tenderness of the feet gradually declines also, and in uncomplicated cases of moderate severity all the visible manifestations of the disease have disappeared within ten or fourteen days after the onset. In young animals, liberally fed, the former good condition is usually rapidly regained after an attack of foot-and-mouth disease; but complete recovery is much slower in older animals, and particularly in milch cows.

The symptoms in sheep are generally somewhat different from those just described, inasmuch as in them the mouth-lesions are frequently slight, while those of the feet are constant and severe. Thus, the chief symptom is great lameness, associated at the outset with suspension of rumination, refusal of food, and febrile disturbance. The pain in the feet is so great that the animal is unable to gather its food, and lies persistently, with consequent rapid loss of condition. The lesions in the feet are much aggravated if the sheep be driven long distances on hard roads, and in such circumstances "casting of the hoof" frequently results.

In pigs, as in sheep, the feet symptoms predominate. The animals lie persistently in their litter, and when forced to move they frequently squeal from the pain in their feet.

Transmissibility to Man.—That the human subject may contract foot-and-mouth disease is proved by many well-attested cases, of which a few may here be cited.

As early as 1834 three German veterinary surgeons made themselves the subjects of an experiment in which each of them drank daily about a quart of milk from cows affected with foot-and-mouth disease. On the second day of the experiment premonitory symptoms, in the shape of fever, headache, and itching of the hands and fingers were manifested in one of them. Five days later a vesicular eruption formed on the mucous membrane of the tongue, cheeks, and lips, and on the skin of the hands and fingers. The other two experimenters were similarly attacked, save that the eruption was confined to the mouth.

In this country numerous cases of the transmission of the disease were noted by veterinary surgeons during the first few years after its introduction. In most of these cases infection took place by means of milk from affected cows, but instances of infection by inoculation were also observed. One of the most interesting of these is recorded in the *Veterinarian* for 1831 (p. 152). The patient was a farmer who had injured one of his fingers in drenching a cow suffering from foot-and-mouth disease. The wound took on an unhealthy action, and after some days he was taken ill with a cold shivering-fit. This occurred in the

evening, and by the following morning the cold fit had been succeeded by fever. Twenty-four hours later an offensive discharge from the nose set in, and vesicles formed on the gums and tongue. In the same journal for 1842 (p. 93), a correspondent states that he and all his family and domestics were attacked on the lips and in the mouth in consequence of using the milk of his diseased cows. Professor Clifford Allbutt informs me that during the epidemic of 1883 he was called to a country house in Yorkshire to see three sick children, in whom he was able at once to diagnose foot-and-mouth disease. The disease, so far as he remembers, was in the mouths of the patients only, but he did not see the patients again. The presence of this disease in the district was ascertained, and the milk consumed by the children came from neighbouring farms, where ample sources of infection existed. He heard that the children made a good recovery. After the diagnosis of these cases some others were reported to him by medical men in the same district. All seemed to be of a comparatively mild character.

During the German epizootic of 1892 numerous instances of transmission of the disease to human beings by means of milk were reported. In a considerable number of cases milkmaids contracted the disease through inoculation of the hands in the act of milking; and in one such instance vesicles formed on the breasts as well as on the hands. Many persons who had to handle or attend to diseased cattle contracted the affection by bringing their dirty fingers into contact with the lips. A shepherd was infected by holding in his mouth the knife which he had used to pare the feet of diseased sheep. A veterinary surgeon who contracted the disease had from 30 to 40 vesicles on his hands; and a workman who had to dress the feet of diseased cows had, besides an extensive eruption on both hands, a severe inflammation of the conjunctivae. A child of a year old, which had consumed milk from diseased cows, sickened with fever and gastric disturbance, followed by the formation of vesicles on the lips and tongue and between the fingers and toes.

The following two cases shew that the virus may retain its activity in butter:—

On the 18th of November 1890 a veterinary student in Berlin had sent to him by his brother-in-law a packet of fresh butter made from the milk of cows suffering from foot-and-mouth disease. On the following day he ate some of the butter for the first time. During the next night he was feverish, and on the morning of the 10th he found his lower lip red, swollen, and completely covered with vesicles as far as the chin. The vesicles were somewhat itchy. Subsequently vesicles formed on the tongue and on the right ear. During the first eight days the parotid and sublingual salivary glands were slightly swollen, and the amount of the salivary secretion was increased.

In 1892 a German clergyman became affected after consuming butter made from the milk of his own cows, which were suffering at the time from foot-and-mouth disease. The disease was ushered in by slight rigors, diarrhœa, and itchiness of the skin; and on the third day numerous

vesicles formed in the mouth, and on the face, neck, breast, and arms. The eruption healed up at the end of ten days.

It is not improbable that some outbreaks of so-called "stomatitis epidemica" in mankind may turn out to be foot-and-mouth disease; and in all cases of such a character careful inquiry should be made into the possibility of the infection.

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HYDROPHOBIA

By Prof. G. Sims Woodhead, M.D.

Synonyms—*Rabies* (in animals); Lat. *Lyssa*; Fr. *La rage*; Ger. *Hundswuth*, *Wasserscheu*, *Tollwuth*.

Hydrophobia, like glanders, is a disease usually contracted by man through infection from one of the lower animals. It is then associated with an injury, such as the bite of a dog, and the inoculation of the broken surface with the saliva of an animal affected with declared or latent rabies. This is the so-called rabies of the streets: wolves, cats, foxes, horses, cows, and deer may also contract the disease: monkeys, rabbits, and guinea-pigs are all inoculable with it, as indeed are all warm-blooded animals.

We have information concerning rabies as early as the fifth century B.C. Democritus of Abdera then described it as an inflammation of the nerves, resembling tetanus, in so far that it was accompanied by severe spasmodic contractions of certain muscles. Xenophon and Aristotle both refer to this disease, the latter noting that it is transmitted from one animal to another by a bite. Keirle notes that Ovid mentions it, as do also Virgil, Horace, and Celsus; the latter speaking of it as "a miserable kind of disease, in which the sick man is at the same time tormented by dread of food and water, in which condition hope is reduced to a narrow limit." Plutarch, in the first century A.D., and Galen, A.D. 131, both mention it, the latter describing it as "the worst of all diseases." Coming down to the Middle Ages, the various authorities added little to our knowledge of rabies or hydrophobia; but in 1709 Boerhaave, and in

1771 van Swieten, commenced a new era of observation. The latter author, in his *Commentaria*, draws attention to the pain that occurs near the bite as a premonitory symptom, describing it in certain cases as like an aura radiating along the nerve. Further, he describes a case of hydrophobia in man, and records that death was not preceded by convulsions or struggles, but appeared to be the result of a general paralysis. Magendie and Bouchet, in 1813, induced rabies in dogs by inoculating them with the saliva of a patient suffering from hydrophobia; this was repeated by Reynault. In 1820 Marochetti noted the occurrence of small nodules or vesicular pustules on the under surface of the tongue, just at the openings of the salivary glands; these appeared from the third to the ninth day after the bite; he stated that if these little nodules were opened and cauterised with a red-hot needle within twenty-four hours and sundry gargles were used, the patient might recover,—thirty-eight of his cases having been cured by this procedure; while if not so treated, the poison contained in them was re-absorbed and the patient died. Morgagni, however, was not satisfied that these results had been obtained. The notion of the spontaneous development of rabies in man was very early scouted, but the spontaneous evolution of the disease in the dog was accepted up to a comparatively recent date. It is now rejected by all who have had any experience of the disease. Virchow had no doubt on the subject in 1855, but it was then known that the saliva or the nervous tissues of a rabid animal injected hypodermically was capable of propagating rabies from man to the lower animals and from one animal to another.

It has been stated that no land or country is free from hydrophobia; but it is interesting to note that in the United Kingdom between the years 1899-1904 there have been only two cases of hydrophobia in the *human subject*. Both of these occurred in the year 1902, one in London, the other in Carmarthenshire. This immunity is, in all probability, the result of the careful application of the muzzling order and of the rigid licensing laws concerning dogs. Between the years 1889 and 1898 there were 104 deaths from hydrophobia, 30 of these in 1889 and 20 in 1895. In 1896 the numbers had fallen to 8, in 1897 to 6, in 1898 to 2, and of the following six years, as we have noted, five were entirely free from death from this disease,—a most satisfactory state of affairs. In other countries, however, the campaign against the disease has not been nearly so successful; and on the Continent and in America much work is still being done on hydrophobia, especially in relation to its diagnosis and treatment in animals. It is for this reason that we have to refer to the workers in these countries for most of the recent observations on rabies.

A much larger proportion of men and children are affected with hydrophobia than of women; this is undoubtedly because the latter, both from their mode of life and from the nature of their clothing, are much less exposed to the bites of rabid dogs.

In Great Britain and Ireland the disease is confined among *animals* almost entirely to the carnivora; and though it was somewhat rife in

Ireland, England, and Scotland, it is now found in certain districts only. In 1893, 94 cases occurred in eighteen counties of England and Scotland; whilst in 1894 no fewer than 248 cases of rabies in dogs were reported; and in 1895 there were 672 cases. In addition, 55 other animals, including 5 cats, were attacked with rabies. In 1893, 46 of these cases came from Scotland; in 1894, 29; and in 1895, 4 only.

In 1895 most of the cases occurred in Yorkshire, especially the West Riding with its 308 rabid dogs and 30 other animals, including 5 cats, and in Lancashire (130); then follow after a long interval Edinburgh (45 cases), Cheshire (31 cases); and then come London, the "Home" counties, Ayrshire, Lanarkshire, Dumbartonshire, Hants, Essex, Cornwall, Stafford, Durham, Northumberland, Cumberland, Derbyshire, Northampton, Warwickshire, Lincolnshire, Notts, Salop, and Hereford.

In the metropolitan district there were in 1889 no fewer than 176 cases; in 1890 the number of cases had fallen to 44, in 1891 to 28, and in 1892 to 3; this fall corresponded to, and was continuous with, the enforcing of the muzzling order. As soon as the order was allowed to lapse, a rise in the number of cases began, and continued until the order was reinforced. Since that date there has been a steady fall in the number of cases amongst animals, and a corresponding diminution in the number of cases in the human subject.

Etiology.—The poison, whatever may be its nature, is usually contained in the saliva; and as early as the beginning of the last century experimental rabies was produced in the dog by inoculation with the saliva of a hydrophobic patient. The toxic material appears to be excreted in the saliva of the parotid gland, and in less degree by the other salivary glands, the lacrimal glands, the pancreas, and the mammæ of rabid animals. The poison may also be found in the suprarenals, and in the fluid and substance of the cerebrospinal nervous system, especially the medulla oblongata; it is found also in the peripheral nerves, though in much smaller quantities than in the central nervous system. It was supposed at one time that the blood was not infective, but Marie states that the blood, when given in large quantities, may set up infection. The saliva of a dog has been found to contain the toxic material three days before the disease has manifested itself.

That hydrophobia is due to some form of organism possessing the power of multiplying in the tissues and of producing a toxic substance, which, as in the case of tetanus, appears to act specially upon the central nervous system, can now scarcely be doubted, and it is possible that Negri's bodies (*vide* p. 822) constitute the virus. As in other specific infective diseases the virus is transmitted directly from animal to animal through the medium of some fluid or secretion. In rabies, too, there is a period of incubation, during which the poison appears to increase in quantity. In this respect it is unlike snake-bite, after which the symptoms come on with excessive rapidity. The whole history of a case of hydrophobia so much resembles a case of tetanus in all essential details, that, unlike as the two diseases are in certain respects, the demonstration of a microbic factor

in the one naturally suggests the presence of a similar factor in the other. Micrococci of various sizes, aerobic and anaerobic in their growth, presenting different appearances in cultures, and staining by different methods, have been associated with this disease; but when it has come to a rigid proof of the causal connexion of a particular organism with the disease, the chain of evidence has invariably broken down at some critical point. In 1897 G. Memmo announced that he had obtained pure cultures of a blastomyces from the brains of six rabbits that had succumbed to experimental rabies; and also from the brain of a four-year-old child which had died from hydrophobia set up by the bite of a mad dog. On culture media this organism is said to grow slowly when first taken from the animal, but in succeeding generations its growth is much more luxuriant and definite. The organism described appears to assume an intermediate position between a saccharomyces and an oïdium. It is certainly pathogenetic in animals, its incubation-period is comparatively prolonged, and it gives rise to paralytic symptoms; but whether it be the immediate cause of rabies is still doubtful. Bruschettini, using new culture media—agar or bouillon containing lecithin, cerebrin, and other substances normally present in the nervous system, and defibrinated dog's blood—was able, by inoculating with small fragments of the nervous system of a rabbit that had died after injection with "virus fixe," to obtain in from 24 to 36 hours a group of small, transparent, drop-like, confluent colonies very slightly elevated above the surface of the special medium. Bruschettini maintains that he has isolated an organism—a short thick bacillus, resembling Fränkel's diplococcus, or in older growths like the diphtheria bacillus,—which by its biological characters may be distinguished from all other micro-organisms; that it constantly sets up the classical form of experimental rabies; that it is possible to find it in the nervous system of rabid animals, and that he is justified in regarding this microbe as the specific cause of rabies. On the other hand, so general has been the failure to trace this hypothetical organism by any of the ordinary methods used in bacteriology, that it has been suggested that the causal organism may belong to the animal kingdom, and resemble the minute animal parasitic organisms associated with malarial and other diseases. Negri's observations appear to support this hypothesis. It would appear, at any rate, that the conditions for the growth of this organism, whatever its nature, are best supplied in the cerebrospinal system; for not only is the poison found more especially in the nervous structures, but they seem to be specially attacked.

Pasteur, recognising this, proceeded in his experiments to prepare cerebrospinal fluid, and an emulsion of the medulla oblongata or of the spinal cord in saline solution or broth; with these emulsions he injected animals subcutaneously, subdurally into the brain, or into the muscles and nerves of the limbs. By these means he was enabled to produce rabies with certainty in dogs, rabbits, monkeys, and other animals, the severity of the disease being determined apparently by three factors: (*a*) the quantity of the rabic virus introduced; (*b*) the point of its introduction; (*c*) the strength of the virus as determined by the kind of animal which

affords the cultivation ground for the growth of the hypothetical organism. The quantity of the virus is readily measured by making a series of dilutions; for this purpose Högyes used salt solution, and Bardach simply distilled water—the former mode of dilution apparently being the one to be preferred.

It is a matter of common observation that slight wounds made with the teeth of a rabid dog in the skin of the limbs and of the back are often followed by the disease after an extremely long period of incubation; whilst in the case of lacerated wounds of the tips of the fingers, where small nerves are numerous or where the muscles and nerve-trunks are reached, or of lacerated wounds of the face where there is a similar abundance of nerves, the period of incubation is usually much shorter and the disease more severe. When material from the rabic nerve-centres of a dog or of a human being is injected into the anterior chamber of the eye, or under the dura mater, the animal so inoculated passes through a severe attack of rabies, and dies in from twelve to fifteen days. The disease may be induced with certainty when the rabic material is injected directly into a mass of muscle; or, as has already been stated, into a peripheral nerve. It will thus be seen that the two sets of conditions, natural and experimental, run in parallel groups, the severity of the disease being usually determined by the ease with which the poison can make its way to the central nervous system. It has been assumed, indeed, by Tizzoni and Centanni that, as the lymph-channels of the nerves are more directly in communication with the lymph-spaces in the cerebrospinal canal than are other lymph channels, any poison introduced directly into them is soon carried into positions where the conditions are favourable for multiplication and action on the nerve-centres; and is thus enabled to determine a severe attack of the disease at an earlier period than when the poison is introduced elsewhere, unless indeed it be injected directly into the cerebrospinal system. Absorption of the rabic poison may take place even from a healthy mucous surface; and the conjunctiva and the nasal mucous membrane have both been noted as unabraded surfaces from which such absorption has taken place. It is stated also that the rabic poison may be transmitted from the mother to the fœtus; and several experiments are recorded in which this has actually been brought about: it appears to be quite possible, moreover, that in such a case the absorption of a toxin may readily take place through the placenta without any transmission of the organisms which produce the poison. Babes, however, denies its presence in the brain of the fœtus in utero. It has been found that the filtrate taken from an emulsion passed through a porcelain filter, when injected into a dog, may produce distinct paralytic phenomena. In consequence of this observation rabies has been defined as a toxoneurosis, but from the statement as to the passage of the minute plastic Negri bodies through a Berkefeld filter (*vide* p. 823), such a definition must be looked upon with suspicion.

A very important point in this connexion is that, if the spinal cord

of a dog be cut across before injection of the rabic poison is made into one of the nerves of the hind foot, it will be found that if, after the disease has had time to manifest itself, two portions of the cord be taken, one below and the other above the point of section, only the emulsion made of the lower portion of the cord will, when used for inoculation, set up rabic symptoms. The same holds good when a similar experiment is made by injecting the poison into the nerve of a fore limb, the upper portion of the cord now inducing rabies. It is interesting, too, to observe that when the disease is developed slowly as the result of a bite in a limb on one side of the body, the peripheral nerves on the opposite side may also contain the rabic virus; and, if used as material with which to inoculate another animal, may set up a more or less virulent form of the disease. It must, then, be concluded that in order to determine the severity of a case it is necessary first to answer these two questions: (i.) Was it possible for the poison, say, from the saliva covering the teeth of a rabid animal, to make its way into the wound? and (ii.) Could this poison make its way to the nerve? In many cases the rabic virus may be cleansed from the teeth by the clothing which covers the bitten part; hence it is that patients bitten by animals undoubtedly rabid often escape the disease, as the leather, cloth, or other clothing material has cleansed the teeth before they came in contact with the skin. It was pointed out by Pasteur and by Sir V. Horsley that rabbits, when etherised and then presented to a mad dog to be bitten on the fur, in a very large proportion of cases escape the disease, although the teeth may have passed well through the skin: if, on the other hand, the part presented to the rabid dog be shaved before it is bitten, a much larger proportion of the bitten animals contract rabies. From what has already been said, it is also evident that, where the skin is thick and the nerves few, a small quantity of virus may find its way into a wound, but does not penetrate into the nerves, and the patient may suffer no evil effects beyond those due to the bite itself. This explains why only about 16 per cent of the cases bitten by rabid animals appear to contract hydrophobia.

Morbid Anatomy and Histology.—On autopsy nothing very characteristic of the disease is found; the main features observed are darkening of the blood, congestion and catarrh of the fauces, larynx, trachea, lungs, pharynx, œsophagus, and stomach; in the mucous membrane of the latter, according to Bristowe, hæmorrhages may be found. In the dog the teeth are often broken, and the tongue and buccal mucous membrane are lacerated and inflamed. The small vesicular pustules sometimes seen on the under surface of the tongue are said to be due to the accumulation of secretion in the obstructed glandular canals. There is also marked congestion and œdema of the central nervous system and the meninges; there may be acute meningitis with a distinct effusion of lymph and even minute hæmorrhages, and fluid in the ventricles is not of uncommon occurrence: small extravasations of blood have been noted in the spinal cord. On microscopic

examination it is stated that there is a migration of leucocytes into the perivascular lymphatic spaces and into the connective tissue of the nerve-centres. Microscopic hæmorrhages have also been found; Sir W. Gowers and others point out, and I have corroborated this, that such hæmorrhages are specially well marked near the floor of the fourth ventricle; but according to Sir V. Horsley they may occur at different points in the central nervous system, so that the whole must be examined. Hyperæmia, hæmorrhages, and areas of softening of the grey matter of the anterior and posterior horns have been described; also strands of degeneration of the white matter of the columns of Goll and of Burdach in the cervical region when the bite was on the hand, in the lumbar region when on the lower limb. Gombault and Schaffer describe great emigration of leucocytes into the anterior horn especially in the perivascular lymphatics. The nerve-cells in this position are said to undergo degenerations of various types, pigmentary, hyaline and granular, and vacuolation. There may also be degeneration of the nerve-sheath and enlargement of the axis-cylinder accompanied by infiltration of leucocytes in the nerves passing from the site of the bite. Congestion of the peripheral nerves and of the sympathetic system has also been described; and both Coats and Elsenberg pointed out that in some cases, in addition to the migration of leucocytes in the medulla oblongata, there is an accumulation of leucocytes in the salivary glands—especially in the parotid, in the mucous glands of the larynx, and in the kidneys; this condition being associated with the marked congestion that occurs in these positions.

Prof. Clifford Allbutt in 1872 described vascular congestion, hæmorrhages, transudation, thickening of the walls of the vessels, patches of nuclear proliferation and degeneration, and disappearance of nerve-strands in the cerebrum, medulla oblongata, pons, and spinal cord; and indicated that all these changes may be regarded as pointing "to the action of an animal poison acting primarily on the cerebrospinal nervous system." He pointed out that in order of severity the pathological lesions are greatest in the medulla; then follow in order the cord, the cerebral convolutions, and, lastly, the central ganglia of the encephalon: whilst the order of symptoms during life, as he maintains, corresponds fairly definitely to this order of affection: "first, intense reflex irritability in the region of the medulla, with no tetanic symptoms and no delirium; secondly, increasing hyperæsthesia throughout the cord, with semi-tetanus; thirdly, delirium."

Sir W. Gowers noted a granular appearance in many of the nerve-cells, and "adjacent to or around many cells were spaces, in some cases apparently empty, in others containing granules." He also noted the presence of pigment-granules in some nerve-cells and of *corpora amylacea*. (This is a very interesting observation in view of Negri's recent work. See p. 822.) In some of the smaller vessels he found thrombi, and in the perivascular lymphatic sheaths he described numerous small cells—migrated leucocytes—so densely packed as to cause actual compression of the vessels. To some of these collections, often situated "in the

respiratory centre of the medulla," he gives the name of "miliary abscess." He concludes that "there is certainly nothing in the histological characters of the lesions which can be regarded as specific of the disease. The collection of cells in the perivascular sheaths has been observed in other diseases . . . but the distribution of these lesions, their intensity in the lower part of the medulla and in the neighbourhood of certain nerve-nuclei is, as far as I am aware, peculiar to the disease, and constitutes a distinguishing anatomical character."

Several authors maintain that the hyaline or hyaloid degenerations described by Benedikt are found in similar positions in aged dogs and in various other diseased conditions.

Lütkemüller found a moderate leucocytosis in rabid animals, accompanied by the presence of an extraordinary number of microcytes.

Golgi found certain alterations of the nerve-cell—vacuolation and swelling on the one hand or diminution in size on the other, swelling and loss of sharp outline of the nucleus and changes in the chromatin particles. In addition, by means of his silver method he brought out certain alterations in the nerve-cells and their dendrites—"diffuse swelling," atrophic changes with loss of substance, a process of progressive atrophy which proceeds apparently from the cellular body and involves the processes to the finest extensions of the protoplasmic branches. The cells lose their homogeneousness, appear granular, and present diffuse swellings producing a varicose condition. The axis-cylinders also shew beaded swellings. A peculiarity of the process is that the abnormal alterations of the elements are not diffused through every portion of the central nervous system, but are focal, there being zones with altered cells and others without any modification of the nerve-elements." H. J. Berkley continuing Golgi's observations obtained results which, whilst agreeing on certain points, were in some respects different. He found that "degenerated cells were universally present in every portion of the cortex," instead of being focal only; further, swelling of the dendrites does not start from the cell but "begins at the periphery and extends centralwards or all the component members of the cell undergo necrosis synchronously." The swelling of the axis-cylinder fibre is rare. There are frequent tumefactions along the stems of the dendrites, the swellings being small, "the portions of the dendrites between the swellings are thin, and have but very few of the gemmules still adherent to them, and of those remaining, still fewer shew perfect staining. On the swellings the lateral buds have completely disappeared, and left no trace of their former presence. A very careful search had to be made to discover any completely normal cells among the diseased ones." The bodies of the cells, says Berkley, are rarely degenerated and changes in the blood-vessels and in the neuroglia are usually comparatively slight. The Purkinje's cells with their processes are less affected than are those of the cerebellum.

Germano and Capobianco find that the lesions described by Golgi, although not pathognomonic are nevertheless (especially as regards their

distribution) constant in the various forms in which they manifest themselves, from the simple hæmorrhage up to the destruction of nerve-cells and the marked hyperplasia of the neuroglia. Moreover, these lesions are constant in character, in order of appearance, and in specially affecting the motor tracts. In rabid dogs and rabbits constant anatomical changes are found, uniformly distributed in the various sections of the cord; the motor regions, as above noted, being specially affected by an acute inflammation of the nervous tissue, which results in degeneration of the nerve-cells and even in complete disappearance of this element; the neuroglia and the myelin sheath undergo simultaneous changes which apparently are in intimate association with one another. The small neuroglia-cells become much larger and more visible than in the normal state. The intervertebral ganglia shew marked congestion, an accumulation of leucocytes, and vacuolar degeneration of the cells. In the nerve-cells of the cortex Nissl's granules become less marked, and atrophy and sclerosis take place.

Babes, in October 1895, after noticing the congestions of various parts of the alimentary tract, describes very minutely the lesions in the central nervous system as falling into two groups: (i.) the more diffuse alterations; general œdema and hyperæmia as a result of commencing inflammatory changes around the blood-vessels; (ii.) the more definite and localised changes; such as dilatation of blood-vessels and hæmorrhages in proximity to the central canal, in the floor of the fourth ventricle, especially immediately under the ependyma, and in various parts of the mucous and serous membranes. Hyaline swelling of the walls of the blood-vessels, and proliferation of their endothelium, leading to obliteration of the lumina, are met with. The nerve-cells next suffer, there is distinct swelling, whilst small hyaline bodies, circumscribed by a pale zone or by vacuoles, appear near the nucleus. Leucocytes fill up the pericellular space, crowding on the nerve-cells, the nuclei of which ultimately disappear.

It will be noted that up to this point none of the histological investigations have shewn anything really characteristic of rabies. Every one of the features mentioned may, as pointed out by Berkley, be observed in some form or other of intoxication. Van Gehuchten and Nelis, however, describe the presence of certain definite and characteristic lesions in the peripheral, cerebrospinal, and sympathetic ganglia. On comparing a section of a normal Gasserian ganglion with one taken from a rabid animal they found that, whilst in the former the large nerve-cells lay near to one another, completely filling the endothelial spaces in which they lay, in the latter many of these nerve-cells had disappeared and been replaced by masses of small round cells which seemed to fill and distend the endothelial spaces, in some cases this "replacement" going on until all the nerve-cells had been destroyed, and the alveolar appearance to some extent lost, the ganglion now appearing to be made up of small cells with, here and there, the remains of an atrophied nerve-cell. In many instances there was also a pericapsular accumulation of new cells,

or this might be the principal feature. This change although characteristic in all species is more marked in the dog than in man, but less in the rabbit. Moreover, in the rabbit and the dog the lesions are always more marked in the cerebral than in the spinal ganglia, and most of all in the nuclear ganglia of the vagus nerve. These appearances are said to be pathognomonic, and as the results may be obtained almost at once (within a few hours) they are, in positive cases, even more useful in diagnosis than, though not quite so certain as, inoculation experiments.

In 1903 Negri described certain bodies which he found included in the cytoplasm of the nerve-cells or in their branches, or rarely lying outside them. In sections they are described as rounded or oval forms, having a homogeneous, oxyphil "ground substance" containing a central body surrounded by granules. Such bodies are found in nearly 100 per cent of the cases of rabies in the dog. These, he maintains, are protozoa, and are in all probability the specific cause of rabies. They are present in the ganglion-cells of the brain, spinal cord, and ganglia, and vary in size from 0·5 to 18 or 20 μ in diameter, the size increasing with the prolongation of the disease. The large forms are seldom met with in specially susceptible animals; the size, moreover, appears to accord with some special stage of development of the organism. These bodies vary very considerably in shape; some of them are round, others more or less elongated masses of protoplasm, others again triangular or slightly spindle-shaped; in some cases small buds may be seen growing from the larger mass; in others the large mass may be constricted in the middle, or if it be somewhat elongated there may be two or three constrictions; sometimes several of these organisms are seen lying together, and are arranged as if they had originally formed parts of one larger organism. These inclusions may be met with at certain stages in almost all the nerve-cells throughout the central nervous system, in prolonged cases of hydrophobia, but they are found most readily and in greatest abundance in the cells of the cornu ammonis. They are also found in the Purkinje's cells of the cerebellum.

These organisms may be stained in either smear preparations or sections. Frothingham recommends Mallory's methylene blue and eosin stain for sections; Williams and Lowden, who recommend the same stain for smears, carry out this method as follows:—"The smears are fixed in Zenker's solution for ½ hour; after being rinsed in tap-water they are placed successively in 95 per cent alcohol plus iodine ¼ hour, 95 per cent alcohol ½ hour, absolute alcohol ½ hour, eosin solution 20 minutes, rinsed in tap-water, methylene blue solution 15 minutes, differentiated in 95 per cent alcohol for 1 to 5 minutes; dry with filter-paper." The cytoplasm of the body is a magenta colour, light in the small bodies, dark in the larger; the central bodies and chromatoid granules are very dark blue, the nerve-cell cytoplasm a light blue, the nucleus a darker blue, and the red blood-cells a brilliant eosin tint. Giemsa's solution is also an excellent stain. One drop of the stain to every c.c. of distilled water, made alkaline by the previous addition of one drop of a 1 per cent solution of potassium carbonate to 10 c.c. of water, is poured over the slide and allowed to stand for ½ to 3

hours (they are not overstained even in 24 hours), wash in running tap-water for 2 or 3 minutes and dry with filter-paper. The cytoplasm of the body stains blue, the central body and chromatoid granules a blue red. The larger bodies have usually a somewhat darker blue than the smaller; the nuclei of the nerve-cells are stained red, the nucleoli a dull blue. Other methods of staining are given by Frothingham and by Williams and Lowden, to whose paper the reader is referred for further details. The Negri bodies retain the eosin with varying intensity, they usually shew structure in the form of unstained ovals or circles, or small dots or rods, within the body, red or blue, according to the method of staining used.

These inner bodies vary in structure and staining qualities, but are principally basophil, and may be in the form of reticular masses, rings, rods, or points; they are usually situated within vacuoles. In fresh smear preparations their homogeneous cytoplasm offers no evidence of a reticulum or of a granular structure, and is distinctly basophil in its staining reactions, whilst the central bodies are surrounded by no clear space, as they sometimes are in sections. It is different in structure and also in staining reaction from the chromatoid granules which surround it, in fact the structure of the central body is that of a protozoan nucleus. The chromatoid granules are most frequently arranged in a more or less regular circle round the nucleus. The shape of the bodies varies enormously, their substance appearing to be exceedingly delicate and plastic, readily adapting itself to the positions in which it finds itself. They are easily destroyed by artificial means, but appear to grow exceedingly rapidly and to multiply or divide at a great rate. "The elongated forms contain from two to five, or even six, nuclei, and are the result of rapid nuclear division without corresponding cell-division"; "under the most favourable conditions—fixed virus—growth and division occur most rapidly and simply, the tiny forms dividing and redividing apparently indefinitely."

Williams and Lowden have demonstrated the presence of these organisms at a much earlier stage than that at which they have previously been found, and they maintain "that the bodies may be found soon enough and in practically large enough numbers to account for the beginning infectivity of the nerve-tissues, and that with only a little more careful experimenting this may be brought out clearly." They believe, too, that although organisms cannot be demonstrated in the blood or in the saliva, this is only because of the small numbers present and not because they are absent. They maintain that these Negri bodies are specific to hydrophobia or rabies, that they are found in large numbers in fixed virus, that they are present in sufficient numbers before the beginning of definite symptoms to account for the appearance of infectivity in the host tissues, that very minute forms barely visible under a 1500 diameter magnification have been made out, and that as these are of great plasticity they may readily pass through the comparatively large pores of Berkefeld filters; they look upon them as living organisms and probably as belonging to the protozoa. In no other disease have bodies similar in

appearance to the Negri bodies been found, and when they are found in sections or in smear preparations the diagnosis of hydrophobia may be made with certainty. All American observers seem to agree then that when these bodies are found, and when van Gehuchten's changes are noted in the ganglia, it is unnecessary to apply the biological test, but that when there is any doubt in the matter the biological tests may give additional information.

Incubation.—The first symptoms of rabies may follow inoculation after intervals of from three to six weeks, but this incubation-period may extend over twelve or even eighteen months; fourteen days on the one hand, and two or even five years on the other, have been given as the extreme limits of the incubation-period. It may be accepted that as a general rule the incubation-period lasts from twenty to sixty days, and that of the very prolonged periods recorded some, at any rate, rest on comparatively untrustworthy information, though one case treated with vaccin passed through an incubation-period of twenty-seven months. The period seems to vary according to the susceptibility of the patient, the virulence of the disease in the animal inflicting the wound, the amount of virus introduced, and the number and position of the bites. Meanwhile there may be no symptoms of any kind, and the wound heals well with little local or general disturbance. At the end of the period of incubation the wound becomes uncomfortable; there is itching, tingling, and a sensation of local heat which may be almost unbearable; this is usually accompanied by a sharp, stinging pain which may be localised in the wound, or may follow the course of the nerves; sometimes the wound becomes livid or opens up afresh and assumes an unhealthy purulent appearance, but apparently not more frequently than do non-rabic wounds. The small vesicles which sometimes occur around the wound, or on each side of the tongue on its under surface (Marochetti) are the only external anatomical lesions which have been described, and they occur comparatively rarely.

Symptoms.—During the early stages, as the disease declares itself (prodromal stage, which lasts for from two to five or six days), the patient is feverish and very thirsty; he becomes exceedingly depressed, anxious, irritable, and has a peculiar hunted look in his eyes; the muscles of the face are drawn and restless, and there is marked pallor. Mr. Makins, taking Bristowe's account as his basis, well describes this stage, and is corroborated in almost every detail by A. Marie. The patient may talk freely, the sentences being sometimes interrupted by sighing inspiration; he usually shews great unwillingness to speak about the possible cause of his illness: sleep is often broken, the patient starting as if suffering from bad dreams; the mouth is dry, with thirst, and disinclination to swallow: loss of appetite, nausea, and epigastric uneasiness and a general hyperæsthesia then come on; the pulse quickens, sometimes becoming very rapid, and the respirations are proportionately hurried and shallow, with now and again a deep breath as though the patient had just been plunged into ice-cold water. On the

second or third day, or even a little later, the symptoms become more pronounced and characteristic, the patient becomes much more excited; he wanders about, is restless and agitated, speaks disconnectedly, and may become slightly and intermittently delirious; he seldom fixes his eyes on anything, and is constantly giving suspicious side-glances, as though on the outlook for some hidden danger; the pallor becomes more marked; the eyes are bright, and the conjunctiva, like the mucous membrane of the mouth and fauces, is markedly congested. On the congested mucous surfaces there is usually an accumulation of thick, tenacious mucus, and in his efforts to expel it the patient emits a harsh coughing sound, which is likened, not very aptly but very naturally, to the barking of a dog. Though thirst is often a prominent symptom there is usually great difficulty in swallowing, especially fluids. At first the patient is anxious to drink, and he makes the most determined efforts to do so; but the moment the fluid comes in contact with the fauces it is expelled with considerable violence, and severe spasmodic contractions of the muscles of deglutition and of ordinary and extraordinary respiration come on: this condition is often followed by a tetanic state, with marked opisthotonos and temporary cessation of respiration. The "tendon reflex" and skin reflexes may be markedly increased. These symptoms may abate, only to recur when another attempt is made to drink; or even on the stimulation of a sharp sound, a touch, a bright light, a strong odour, a breath of air, or the mere sound of water: ultimately indeed, after making one or two attempts to swallow fluid, the very sight of water causes such terror to the patient that he is anxious to avoid it. In some cases "sudden severe throat-spasms have been the first symptoms"; and attacks of vomiting often come on at this stage, greenish-brown liquid being thrown up. The symptoms so noticeable in the dog—the desire to be alone, the suspicion of every movement, the surliness, alternating with periods of extreme excitement—are noticeable also in the human subject. The delirium as a rule is intermittent; the patient rambles, but can be brought back to consciousness and quietness by his attendants, though in some cases he may have maniacal attacks, during which he may attempt to murder those of whom he entertains suspicions. During the early stages of the disease increased sexual desire is often a marked symptom, and in the later stages it becomes still more troublesome. The urine may contain sugar, albumin, or even blood. The repeated attacks, however, rapidly exhaust the patient and if the disease be somewhat prolonged there may be great wasting. "The pulse becomes quick, irregular, and small in volume, and respiration quick and shallow, a deep inspiration often inducing a convulsive attack, tenacious mucus accumulates in the mouth and fauces, articulation is thick; later the convulsive attacks increase in frequency, and death from asphyxia may occur during one of them. In other cases the progress is slower, the eyes "sink," the brow sweats, the lips become blue, and the patient dies of slow asphyxia, or occasionally an almost complete remission of convulsive attacks may precede death from exhaustion, the mind in other cases

remaining clear to the end" (Makins). Sometimes a condition which corresponds to the dumb or paralytic rabies of animals supervenes, or may be present from the outset. Following the maniacal or furious form, the symptoms become less marked, groups of muscles become paralysed, and the movements ataxic and aimless, there may be facial paralysis, hemiplegia, or even paraplegia before the final issue; the pulse becomes "thready," the pupils dilate, and the patient succumbs in a convulsive attack. These paralytic symptoms may in certain cases characterise the attack from the onset of the disease; there is no stage of excitement, and the patient with all the other symptoms of hydrophobia, extreme depression of spirits, shooting pains at the site of the wound, has ataxia, local or general, difficulty of swallowing, and impaired respiration. There are other cases, again, in which the only symptoms are those of Landry's paralysis—an acute ascending paralysis beginning in the lower limbs, and gradually spreading upwards until the muscles of the neck and face are involved. This condition appears to be due to a later extension of the disease to the cord, except in those cases in which the poison from the rabid animal makes its way directly into the veins. It is probably for this reason that the dumb or paralytic form of the disease is so frequently met with in animals in which rabies has been produced experimentally. The course of the disease, from the time of onset, varies considerably in different cases, but in one series of 378 cases (French) more than 33 per cent died on the fourth day, 23 per cent on the second, 18 on the third, nearly 9 per cent on the sixth, and over 5 per cent on the fifth days. Only one case out of the whole series living on to the fifteenth day.

Diagnosis.—The only diseases with which rabies is usually confounded are hysteria, insanity, tetanus, and Landry's paralysis. The first of these can be discarded only after a careful study of the symptoms, and after eliminating the possibilities of infection by the bite of a rabid dog; where patients have been bitten by dogs that were not rabid, and have never manifested any signs of hydrophobia, the diagnosis can of course be settled at once; but in some cases in which hysteria is associated with mania, or in which there is great mental disturbance, the diagnosis is often a matter of some difficulty, a difficulty, however, which as a rule does not extend beyond the fourth day of the disease: under these conditions the patient may (especially if fear of the result of a bite even from a non-rabid animal be the cause of the hysteria) bark and bite or snap almost continuously; but, as has frequently been pointed out, these patients do not suffer from the characteristic respiratory spasm, which, accompanied by a peculiar catching of the breath, is said to be pathognomonic of rabies. Tetanus, which sometimes follows the bite of a dog, may be distinguished by the shorter incubation-period, the tonicity of the spasms, and the contraction of the levatores anguli oris which gives the grinning expression peculiar to tetanus, so different from the haggard, hunted look, characteristic of rabies; the marked rise of temperature that occurs in tetanus is also said to distinguish it sharply from hydrophobia, in which the temperature is never much raised, and may be normal or even

subnormal. Sir W. Gowers, however, maintains that this is not accurate, and says: "At the outset the elevation is trifling (occasionally, indeed, absent), and throughout the disease it may remain moderate, 100° to 101° F. More frequently, as the symptoms increase, so does the pyrexia, and it mounts to 103°, 104°, or 105° F., and may even reach a still greater height just before death, and may continue to rise for a short time after death. A rectal temperature of 108·8° has been observed twenty minutes after death (Handford)." Diagnosis between hydrophobia and Landry's paralysis may be possible only after a careful study of the history of the attack has been made.

Certain other conditions simulate hydrophobia, and hydrophobia in turn has sometimes been mistaken for them. It may be accepted, however, that in any case where the peculiar mental depression is followed by a stage of excitement accompanied by repeatedly recurring pharyngeal and respiratory spasms, induced in consequence of marked hyperæsthesia to light, sound, or shock, the disease can be nothing but hydrophobia.

Some of the above symptoms may be met with during the course of an attack of acute mania, of delirium tremens, of stramonium or belladonna poisoning, and of pressure at the base of the brain, but in none are they all present, and this, with the history and duration of the case, usually settles the matter. Marie points out that where the phrenic nerve is involved, as in pericarditis or in diaphragmatic pleurisy there may be painful and difficult deglutition and even respiratory spasm, but in such cases the other characteristic symptoms of hydrophobia are absent.

The method of diagnosis, used by Pasteur, of injecting small portions of the cord of the animal supposed to be rabid into the subdural space of a rabbit, although sometimes too late to guide us to use any special antirabic treatment, has invariably been resorted to, often merely for the sake of reassuring the patient—especially if he be nervous, irritable, or hysterical. The great and protracted mental strain after a dog-bite is often very greatly relieved when the result of the inoculation is negative; if, on the other hand, positive results are obtained, the patient is no worse off than before, unless it is thought necessary to make him acquainted with the diagnosis. An inoculation is therefore made in every case of suspected rabies, if the dog can be identified and secured.

Rabies in the dog is in many cases very similar in its clinical history to the furious form of hydrophobia in man, except that it does not take the form of hydrophobia. The incubation-period seldom lasts beyond sixty days. Towards the end of this incubation-period there is often a distinct rise of temperature, usually lasting for two or three days; the animal loses its desire for human company, becomes morose and sullen, and hides under sofas and chairs, or in quiet corners. It then becomes more irritable; if at rest it snaps at anything that is presented to it; when left undisturbed it goes about snapping as if trying to catch flies: there is congestion of the mouth, tongue, and fauces, and marked salivation;

the mucus is sticky and readily becomes frothy; the conjunctivæ are red; the animal will often run straight ahead, turning neither to the right nor to the left, but snapping at everything that comes in its way; perverted in appetite, it may swallow any kind of rubbish, so that after death small stones, hay and straw, hair, shavings, bits of wood, and the like may be found in its stomach which in some cases is much distended: the animals do not avoid water, and in association with this it has been noted that there is little or no cutaneous hyperæsthesia. The bark usually becomes changed into a series of characteristic howls, which, beginning with a short low note, ends with a long higher note; it has also a peculiar metallic ring (Gowers). The appetite then begins to suffer, food is imperfectly masticated and finally cannot be swallowed, but the animal never suffers from hydrophobia. Emaciation sets in, and in the later stages of the disease the muscles of the hind limbs and the lower jaw, the latter of which drops, may be paralysed; the muscles of other parts may also be affected.

The paralytic form appears in from 15 to 20 per cent of the cases of rabies; in Turkey almost every case assumes this form. The animal so attacked suffers from most of the symptoms met with in the furious form, but he is quiet, cannot be provoked to bite, is apparently hyposensitive, though sometimes there is evidence of irritation at the site of the bite, the appetite remains good, but the jaws finally become paralysed, especially in dumb rabies, and death takes place in two or three days.

Prognosis.—The percentage of deaths of patients bitten by rabid dogs was given variously at from 5 to 50 per cent before the introduction of Pasteur's treatment.[1] The most trustworthy figures, however, give the mortality at 16 per cent of those bitten by rabid animals. This percentage included practically all those in whom the symptoms of true hydrophobia appeared; that is, those cases were left out of account in which merely subjective pain and other phenomena were ascribed to the wound caused by the bite, and after which nothing more than hysterical symptoms supervened. The patient almost invariably succumbs within four days, sometimes after as short a period as twelve hours after the onset of hydrophobic symptoms.

Treatment.—The old treatment consisted simply in encouraging bleeding from the wound; or first excising the wound or scar and then encouraging the bleeding by means of a ligature, or by warm bathing or cupping-glasses; the raw surface was then freely cauterised with caustic potash, nitric acid, nitrate of mercury, lunar caustic, or the actual cautery. In some cases it was even recommended that the wound should be carefully sucked by a person who, of course, should have no wound or abrasion of the lips or mouth, care being taken to wash

[1] Bollinger states that from a series of collected statistics, it may be gathered that of all patients bitten by dogs undoubtedly rabid, 47 per cent suffer and die from hydrophobia. When the wounds have not been cauterised, 83 per cent of the cases succumb; when they have been cauterised, in some cases not very promptly, 33 per cent die.

the mouth out most carefully between each application of the lips to the wound. It is doubtful whether the disease ever manifests itself after such treatment, when followed immediately by the application of a powerful caustic, and especially if the wound be small. Where no actual wound has been made by the teeth, the part should be carefully washed with some antiseptic lotion. The sufferings of the patients may be relieved by subcutaneous injections of morphine, inhalation of chloroform, or suppositories of morphine. Bromide of potassium, chloral, and Calabar bean are also recommended; three cases of cure are reported as due to curara, a drug which is tolerated in large doses in this condition. Sir W. Gowers recommends doses of $\frac{1}{16}$ to $\frac{1}{2}$ grain, to be given every quarter or half hour until muscular paralysis comes on; this is repeated as the effect wears off. The same author mentions that Polli gave three grains of curara in five and a half hours to a child of twelve years of age. The patient should be placed in a quiet, warm, dimly-lighted room, and carefully watched, the greatest care being taken to prevent inoculation of wounds with his saliva; and should the nurse be bitten by the patient, as sometimes happens, especially during the hysterical and maniacal stages of the disease, the bite should be treated as that of a mad dog. At one time Turkish, Russian, and steam baths (Buisson), and wet packs were also extensively used, but with little or no beneficial result. Tracheotomy has also been recommended when the laryngeal muscles are greatly affected; but as the respiratory muscles soon become paralysed, this measure obviously can give but temporary relief. All general treatment, indeed, is merely palliative, and is usually directed to the maintenance of the strength of the patient. Even Pasteur's antirabic treatment appears in most cases to be unavailing when symptoms of the disease have manifested themselves; but if this treatment can be applied during the early part of the period of incubation, in cases up to the sixth day and, in some cases, even up to the tenth day after the infliction of the wound, a much larger percentage of the cases bitten may end in recovery. When the wounds are severe the greatest care should be taken to keep them clean and properly dressed during the period of Pasteur's antirabic treatment. The patient should be kept from violent exercise, but in the fresh air, his diet should be nourishing but digestible and non-stimulating. During the course of treatment and for some time after it has ceased alcoholic drinks of all kinds should be strictly forbidden.

Pasteur's treatment of hydrophobia is based on the knowledge that rabic virus may be intensified or attenuated at will. He first observed that the tissues and fluids taken from rabid animals varied considerably in their virulence, then that the virus taken from similar positions—say the cerebrospinal fluid—had always the same action in the same species; but that fluid taken from an animal of a different species was weaker or stronger as the case might be. Thus, the cerebrospinal fluid of a series of dogs is of constant strength, and inoculations made from dog to dog regularly produce death from rabies, the animals passing through an incubation-period fairly constant in length, and through a series of similar symptoms

ending in death at the same term. If, however, a series of monkeys be inoculated, the virus gradually becomes more and more attenuated in successive animals until eventually, after the disease has run a longer and longer course, there comes a time at which the virus is no longer sufficiently active to cause death. If this attenuated fluid be now passed through a series of rabbits, dogs, or guinea-pigs, its virulence gradually rises until the original intensity is reached. If successive inoculations be made into rabbits with fluid either from the dog or the monkey, the virulence may be so exalted beyond that of the virus taken from a street dog, in which the incubation-period is from twelve to fourteen days, that at the end of the hundredth passage the incubation-period may be reduced to about seven days, or even to six. This, the strongest virus obtainable, was called by Pasteur the "virus fixe." Rabic virus appears to be attenuated by the action of heat and of certain chemicals. If it be subjected for about an hour to a temperature of 50° C. its activity is completely destroyed, or in half an hour if to a temperature of 60°. A 5 per cent solution of carbolic acid, acting for the same period, seems to exert a similar effect; as do likewise 1 per 1000 solutions of perchloride of mercury, acetic acid, or permanganate of potash. According to Babes, the virus rapidly loses its strength on exposure to air especially in sunlight; when protected from light and air it retains its virulence for a long period. Active virus has been obtained forty-four days after death, and has been obtained from a glycerin extract kept for a month. It is of importance to remember this action of heat and of antiseptic and chemical substances when considering the nature of the virus; for, although permanganate of potash might act simply as an active oxidising agent upon the manufactured toxin, heat and the other chemicals appear to act rather as they are wont to do upon micro-organisms and enzymes. If this be the case, we have additional evidence that the virus is organised.

In his early experiments Pasteur observed that the cords of rabbits that had been dead for some time contained less virulent poison than did the cords of animals freshly killed; this was especially the case when the air was dry and the cord protected from putrefactive processes. At the end of fourteen or fifteen days the rabbit's cord kept under these conditions, completely loses its power of setting up rabic symptoms; in this case the period at which the virus becomes inactive appears to be determined, first, by the dryness of the atmosphere; and, secondly, by the size of the cord; as the more slender the cord the more rapid the loss of virulence. It is possible, however, that this loss of virulence may be due to a diminution in the quantity of virus rather than to any alteration in its quality, and Högyes and Bardach's experiments on the dilution of the virus with saline solution, or with distilled water, appear to indicate that there may be some such ratio of quantity to period of incubation and intensity of attack. Tizzoni and Centanni, by subjecting "virus fixe" to a process of peptic digestion by means of the addition of diluted gastric juice for varying periods, are able to obtain rabic virus of varying degrees of intensity. These methods of attenuation and

intensification have been most carefully worked out; as it was evident that a method of protective inoculation must depend entirely upon the possibility of the production of protective vaccins of different strengths. In his earlier experiments Pasteur selected a series of rabic poisons beginning with that obtained from the spinal cord of the monkey—from the very weak to the strongest that he could obtain in this animal; then passing through a similar series obtained during the process of exaltation of the virus by passage through a number of rabbits. By inoculating dogs subcutaneously with virus taken from a series commencing with the weakest from a monkey, and gradually working up through that obtained from the rabbit—from the earliest to the latest in the series—the animals become immune, not only against subcutaneous injection, but against subdural injection with "virus fixe"; and also against the bite of a rabid dog. Such a method as this, however, had several disadvantages, and was not absolutely certain in its action, only fifteen out of twenty dogs being completely protected. Pasteur, therefore, assisted by Chamberland and Roux, devised a more trustworthy and accurate method. A number of cords cut into short segments, which were held in series by the dura mater, were suspended in sterile glass flasks plugged with cotton-wool, and containing a quantity of some hygroscopic material such as potassium hydrate; each flask with its contents was kept at a temperature of 72° F. (about 22° C.). The cord when taken out at the end of the first twenty-four hours was found to be almost as active as the fresh untreated cord; that removed at the end of forty-eight hours was slightly less active than that removed twenty-four hours previously; and the diminution in virulence, though gradual, progressed regularly and surely until at the end of the fourteenth or fifteenth day the virus was inactive. An emulsion of the cord of the last day was made, and a certain quantity injected into a dog that had been bitten; this was followed by an injection of an emulsion of a thirteenth-day cord, and so on until the animal had been injected with a perfectly fresh and therefore extremely active cord corresponding to the "virus fixe." Animals treated in this way were now found to be absolutely protected, even against subdural inoculation with considerable quantities of "virus fixe"; and protective inoculation against rabies had become an accomplished truth.

As it would be very undesirable to inject any but those persons who had actually been bitten by a rabid or presumably rabid animal, Pasteur continued his experiments in order to see whether it would not be possible to cure a patient already bitten, and, as it were, to steal a march on the virus introduced through a bite. He found that if the process of inoculation be begun within five days of the infliction of the bite, almost every animal bitten can be saved; and that even if the treatment be commenced at a longer interval after the bite a certain proportion of recoveries may still be obtained, and that the "protection" would last for at least two years, and probably longer. Then an opportunity came to apply the treatment to the human subject. The description of the case, that of Joseph Meister, has now become classical. This lad, nine years of age,

was bitten severely on the arms and legs by a mad dog on the 4th July 1885; his worst wounds were cauterised with carbolic acid about twelve hours after the bite. The dog was undoubtedly mad, and it was recognised that under the ordinary methods of treatment there was little chance of the survival of the patient; it was resolved, therefore, to apply the treatment which had been so successful in the case of dogs, and so to give him the only apparent chance of recovery. Thirteen injections were made in ten days: two on the first day with emulsions made from cords that had been exposed to dry air for fourteen and ten days respectively; two on the second day with emulsions of cords that had been exposed for eleven and eight days respectively, and then on each of the following days up to the tenth with emulsions of cords exposed for eight, seven, and six days down to one day; and on the last day with that of the fresh cord of a rabbit in which the virus retained its full virulence. In order to control the results, for every injection that was made into the child a corresponding one was made into a rabbit; and it was found that of the five rabbits so inoculated with the first five injecting materials not one manifested symptoms of hydrophobia; but the other eight all succumbed to the disease, the period at which they died being shorter as the cords exposed to the dry air for shorter and shorter times were successively injected. The patient, thus gradually prepared by the earlier inoculations, was not in the slightest degree affected by the stronger virus; and five years afterwards the boy was still perfectly well.

The chance of success in the human subject appears to be even greater than in the dog or rabbit, seeing that on account of the resistance offered by the human tissues to the virus, the period of incubation is comparatively prolonged; thus there is an opportunity of obtaining immunity if the process of vaccination be commenced soon after the bite has been inflicted, the protection becoming complete before the incubation-period has passed, the virus in the system then having no more chance of affecting the nerve-centres than has the "virus fixe" when injected under the dura mater of a protected animal; the nerve-centres having become gradually acclimatised, as it were, to the presence of the rabic virus, and able to carry on their proper functions even in its presence, until in time, like the microbial poisons, it is gradually neutralised and eliminated from the body. Pasteur afterwards modified the method somewhat, and used injections of cords up to the third day. This "simple" method, as quoted by Marie, is given in the following table:—

[TABLE

Day of Treatment.	Number of Days that Brain had been desiccated.	Dose injected.
1st day	Brain of 14 days	In dose of 3 c.c. of emulsion.
	13 ,,	,, ,, ,,
2nd ,,	,, 12 ,,	,, ,, ,,
	11 ,,	,, ,, ,,
3rd ,,	,, 10 ,,	,, ,, ,,
	9 ,,	,, ,, ,,
4th ,,	,, 8 ,,	,, ,, ,,
	7 ,,	,, ,, ,,
5th ,,	,, 6 ,,	,, 2 c.c. ,,
	6 ,,	,, ,, ,,
6th ,,	,, 5 ,,	,, ,, ,,
7th ,,	,, 5 ,,	,, ,, ,,
8th ,,	,, 4 ,,	,, ,, ,,
9th ,,	,, 3 ,,	,, 1 c.c. ,,
10th ,,	,, 5 ,,	,, 2 c.c. ,,
11th ,,	,, 5 ,,	,, ,, ,,
12th ,,	,, 4 ,,	,, ,, ,,
13th ,,	,, 4 ,,	,, ,, ,,
14th ,,	,, 3 ,,	,, ,, ,,
15th ,,	,, 3 ,,	,, ,, ,,

It was soon evident, however, that, although this method was efficacious when the wounds were not severe and were confined to parts in which the nerve-supply was not extensively interfered with, it was often quite inadequate in serious cases, when the wounds were on the face, or had been inflicted by a mad wolf, the virus of which is considerably more active than that of the rabid dog of the streets. In these latter cases the number of injections which, in the simple treatment, are spread over five days, are made in three days; then, on the fourteenth day, a fresh series of injections, or rather repetitions, is begun, which lasts until the twenty-first day. This "intensive" method is given in the following table:—

Day of Treatment.	Number of Days that Cord had been desiccated.	Dose injected.	Day of Treatment.	Number of Days that Cord had been desiccated.	Dose injected.
1st day, morn.	14 days	3 c.c.	8th day	4 days	2 c.c.
	13 ,,		9th ,,	3 ,,	1·5 c.c.
even.	12 ,,		10th ,,	5 ,,	2 c.c.
	11 ,,		11th ,,	5 ,,	2 c.c.
2nd ,, morn.	10 ,,	3 c.c.	12th ,,	4 ,,	2 c.c.
	9 ,,		13th ,,	4 ,,	2 c.c.
even.	8 ,,		14th ,,	3 ,,	2 c.c.
	7 ,,		15th ,,	3 ,,	2 c.c.
3rd ,, morn.	6 ,,	2 c.c.	16th ,,	5 ,,	2 c.c.
even.	6 ,,		17th ,,	4 ,,	2 c.c.
4th ,,	5 ,,	2 c.c.	18th ,,	3 ,,	2 c.c.
5th ,,	5 ,,	2 c.c.	19th ,,	5 ,,	2 c.c.
6th ,,	4 ,,	2 c.c.	20th ,,	4 ,,	2 c.c.
7th ,,	3 ,,	1 c.c.	21st ,,	3 ,,	2 c.c.

Babes, in order to obtain a constant virus, makes a mixture of cords which have been exposed to the drying process for three or four different periods. He inoculates at least twice a day, and in very severe cases more frequently; moreover, he uses larger quantities of the protective material and continues the treatment over a longer period; he obtains excellent results. It is now generally acknowledged that, when the operation is properly performed, the injection even of very large quantities of virus may be safely carried out.

STATISTICS of CASES treated in the Pasteur Institute, Paris, not including persons in whom the disease declared itself during course of treatment, in which therefore the treatment was not complete.

A. *Cases excluded in which the disease declared itself within a fortnight after inoculation.*

Years.	Persons Treated.	Deaths.	Mortality per cent.
1886	2671	25	0·94
1887	1770	14	0·79
1888	1622	9	0·55
1889	1830	7	0·38
1890	1540	5	0·32
1891	1559	4	0·25
1892	1790	4	0·22
1893	1648	6	0·36
1894	1387	7	0·50
1895	1520	5	0·33
1896	1308	4	0·30
1897	1519	6	0·39
1898	1465	3	0·20
1899	1614	4	0·25
1900	1413	4	0·28
1901	1318	5	0·37
1902	1105	2	0·18
1903	628	2	0·32
1904	755	3	0·39
1905	727	3	0·41

[TABLE B

B. *All cases included in which treatment was completed.*

Years.	Persons Treated.	Deaths.	Mortality per cent.
1886	2682	36	1·34
1887	1778	21	1·18
1888	1625	12	0·74
1889	1834	10	0·54
1890	1546	11	0·71
1891	1564 + 5[1]	9	0·57
1892	1793 + 5[1]	7	0·39
1893	1648 + 4[1]	6	0·39
1894	1392	12	0·86
1895	1523 + 1[1]	5	0·33
1896	1308	4	0·30
1897	1521	8	0·52
1898	1465 + 2[1]	4	0·27
1899	1614 + 2[1]	10	0·61
1900	1419 + 1[1]	10	0·70
1901	1318 + 3[1]	5	0·37
1902	1105 + 1[1]	2	0·18
1903	630	4	0·65
1904	757	5	0·66
1905	727 + 1[1]	4	0·54

The Pasteurean method appears to avail little when the disease has once manifested itself.

It has already been mentioned that when cords of different sizes are desiccated for the same period the results obtained are not always the same, so that samples of the dried virus are by no means constant as regards strength. Högyes, in order to get over this difficulty, mixes the fresh cord with normal saline solution, commencing with a dilution of 1-10,000, and gradually rising to 1-100, making as many as 28 injections of from 3 to 1 c.c. of these diluted cords in 14 days in comparatively mild cases, and 53 similar injections in 20 days in the more severe cases. The same end may be attained by heating the virus. Again, if saliva from a rabid animal or an emulsion of the cord be injected into the jugular vein of a horse or a sheep, the animal not only does not succumb to the disease, but an immunity to the disease, as conveyed by the ordinary mode of infection, is set up. Dogs are not so readily protected in this fashion, but with care even this may be effected. It is assumed that the virus in the large volume of blood may be so diluted that it acts as if saline solution had been added, for it is found that injection into the arterial system (when the dilution cannot be so great) is not nearly so successful as when the injection is made intravenously.

In 1905 Remlinger pointed out that amongst cases of rabies treated by the Pasteurean method paralyses of a severe form sometimes make their appearance. To the uninitiated they are very alarming, but they

[1] These cases are not included in the calculations as the patients died from the results of the bite during the course of treatment.

usually pass off spontaneously, and though of great scientific interest, are of little practical importance. The paralyses affects the lower limbs in almost every instance, and the bladder and rectum are also frequently affected.

It comes on between the eighth and last days of treatment, or within the week following, and is ushered in by slight fever, anorexia, and intense opisthotonos accompanied by violent lumbar pains. These symptoms are followed within twenty-four hours by paresis and weakness of the lower limbs, hesitating and tottering walk, and then by complete paralysis. There may be either hyperæsthesia with increased tendon-reflex or anæsthesia with abolition of the tendon-reflexes. The paralyses of the bladder and rectum may lead to either incontinence or retention. In some cases the paralyses are confined to the lower limbs and to the sphincters. Sometimes the paralysis is of a well-defined ascending type, resembling Landry's paralysis. Acute pains in the upper limbs precede paresis and paralysis of the muscles of these parts. The muscles of the face are often similarly affected, and bulbar troubles such as dyspnœa, tachycardia, dysphagia, etc., may supervene. After a very anxious period for those who have not had experience of this condition, during which it appears that these bulbar troubles might have a fatal issue, the symptoms are arrested ; they become ameliorated, and after from one to twenty days the paralytic phenomena disappear, motor power is gradually and fully restored in about four or five days. More rarely this phase may extend over several weeks. The sphincters are usually the first muscles to recover.

The etiology of this condition is very obscure. In exceptional cases the paralysis, in place of being associated with the alteration in the cord, appears to be associated with changes in the peripheral nerves—the facial or the motor oculi—either alone or along with the nerves of the upper and lower limbs. The interruption of the antirabic treatment appears to have no effect upon the course of the paralysis. According to Remlinger, the paralysis can scarcely be the result of a secondary pneumococcal or streptococcal infection, the invariable recovery and the type of the intoxication being against such a supposition. Nor can it be the result of an intoxication by the products of the cord-emulsion ; otherwise these cases would be of more frequent occurrence in hot countries than in cold, in summer than in winter, and no such incidence has been noted. There is no evidence that the paralyses are hysterical, and the almost invariable affection of the sphincters is certainly against such a supposition. The hypothesis that there is some congestion of the medulla appears to be more reasonable. Laveran suggests that this paralysis may be a symptom of rabies of canine origin attenuated and cured by the Pasteurean inoculation. The exceptional paralytic phenomena accompanied by the pain at the site of the wound lend some countenance to such a view, but it must be remembered that in the great majority of cases these pains are absent. Moreover, in certain instances the pains appear to be most marked at the seat of injection. If these paralytic phenomena were the result of rabies attenuated by the treatment they should occur specially in those cases in which the wounds have been very severe,—on the face, for example, and in which the virus

has come from the wolf, say,—but as a matter of fact most of them have occurred in cases in which the wounds were not severe. Moreover, the paralysis appears from twelve to seventeen days after infection, a period of incubation very short for hydrophobia determined by a bite. Further, in many cases, there was considerable doubt whether the animal that inflicted the bite was really rabid. Finally, it comes on too quickly to be caused by the emulsion of cord with which the patient is vaccinated, unless it be that the emulsified cord contains a rabic toxin which can act quickly and very evanescently. It must be noted, however, that these cases are specially numerous when Babes' intensified method, in which the virus is attenuated by heat, is made use of, seven cases out of the 2850 patients thus inoculated developing this form of paralysis. When, however, a "dilution" method is used not a single case occurred amongst 25,872 patients injected. The paralysis does not appear to be due to neglect or accident during the injection. Out of 24 cases occurring amongst 107,712 persons subjected to the antirabic treatment all were cured but two. As regards prophylaxis, the general condition and temperature of the patient should be carefully attended to and chills, which appear to precede the appearance of the paralysis in many cases, should be carefully avoided. The existence of opisthotonos, with a feeling of weakness in the lower limbs, usually indicates the imminence of this paralysis, and when these appear the wisest course is to stop the antirabic treatment, and not to resume it until the paralysis has disappeared. As far as the treatment of the paralysis itself goes, a good general rule for the medical man is that "the best treatment for these cases is none at all."

As early as 1889 Babes and Lepp had conceived the idea that it might be possible by means of the blood to transmit conferred immunity to rabies from one animal to another. Although the success of these investigators was not great, Tizzoni and Schwarz, and later Tizzoni and Centanni, worked out a method of *serum-treatment*, curative and protective in hydrophobia which is worthy of attention. In this method not the rabic poison itself, but the protective substance formed is injected into the tissues. These observers shewed that the serum of vaccinated animals is capable of neutralising the pathogenetic power of the virus of rabies—"virus fixe"—not only when mixed with it before injection, but even when injected simultaneously, or within twenty-four hours after the introduction of the virus into the body. They shewed also that the serum of a rabbit protects a rabbit better than does the serum of a dog; and they indicated that by their method they were able to attain a higher degree of immunity than could be obtained by Pasteur's method. Taking "virus fixe" as their starting-point they prepared a series of weaker materials by submitting it to the action of gastric juice; beginning with a very weak virus so prepared and using a series gradually increasing in strength, they protected not only rabbits and dogs but sheep against the most virulent rabic poison, even when introduced under the dura mater. By continuing the process they succeeded in twenty days, after seventeen injections, in obtaining such a large quantity of the antirabic

substance in the serum that, if injected twenty-four hours before the poison, even so small a proportion as 1 to 25,000 of serum to body weight would protect the animal. More powerful serum still is obtained when the sheep are revaccinated; the injections in this case are made during the course of twelve days, each injection again consisting of 0·25 gramme of the emulsified cord per kilogramme of the weight of the sheep. This process may be repeated again and again so long as the intervals are sufficient to allow the animal to keep in good condition; of this the best criterion is the maintenance or increase of its weight during the process of vaccination. The best time after the completion of the vaccination process at which to take the blood and separate the serum, which contains the antirabic substance, is probably about the twenty-fifth day after the last of the injections of rabic material.

This method of treatment has thus been brought well into line with that of the other specific infective diseases in which serum-therapy has been employed; and there can be little doubt that if this method be as successful as the process of rapid immunisation of the patient worked out by Pasteur, it has many marked advantages and apparently few disadvantages. (For details see (142).) The process in its two stages differs from that developed by Pasteur and at present in use, in so far that, in place of promoting the formation of the antidote within the body of the patient by a process of vaccination with progressively stronger and stronger virus, this part of the process is carried on in an animal; Babes using the dog, Tizzoni and Centanni the sheep. From animals so prepared the antirabic substance is conveyed, along with the blood-serum in which it is dissolved, which acts merely as a vehicle, to the patient or animal to be treated.

In the second modification, instead of using Pasteur's method of protective vaccination for the animals from which the serum is to be obtained, these authors use a vaccin, which has been modified or attenuated by a process of peptic digestion. The exact action of this digestive process has not as yet been discovered. Is it merely a dilution? Have we to do with a positive reduction in the activity of the poison-secreting organisms, or with such a diminution of the potency of the ferment produced by them, that the tissues are not prevented by their presence from reacting and performing their proper functions? In any case, the activity of the virus is so modified that considerable doses may be injected within a comparatively short period, even when protection has not been carried very far.

This serum, when mixed in definite quantity in a test-tube with a lethal dose of canine virus or "virus fixe" and then injected into a rabbit, so neutralises the poison that there is neither any increase in the quantity of the virus nor any appearance of the symptoms of rabies even in animals kept under observation for so long a period as five months. Again, if the serum be not injected until some time after the administration of a lethal dose of the poison, some alleviation is still obtained: but under these conditions a somewhat larger quantity has to be injected in

order to keep the animal alive. The amount required, however, increases so slightly that if the injection of serum be delayed until the end of the first half of the incubation-period, it is necessary to multiply the dose of the serum some six or eight times only. In this respect the serum treatment in rabies has great advantages over that used in other diseases, such as diphtheria and tetanus.

When the serum is injected in small doses even a comparatively short time before the patient is bitten, protection against rabies is obtained. Such prophylaxis, of course, could only be needed by those frequently in contact with dogs; or by persons working for any length of time with rabic virus. The rabic poison has a very definite selective action; as in tetanus it seems to pick out the nerves and the central nervous system. We find, accordingly, that by selecting the site for the injection of the serum much better results may be obtained, even with smaller doses. Thus, if the serum be injected under the intracranial dura mater, much smaller doses are needed than when the injections are made into the substance of a nerve; and for subcutaneous injection a larger dose of the serum is necessary than must be injected into either of the above positions. The serum, when injected into the nervous tissues, may act at once, possibly by a direct chemical antagonism to the virus; though there is very little evidence from direct experiment in favour of this. On the other hand, as some maintain, the serum in the nerve-centres may act not upon the nerve-cells only, but also upon the cells of the neuroglia, which with its aid, perhaps through some special stimulation, are able to carry on their functions in the presence of even considerable quantities of the rabic virus. It appears to be in some such way as this that the point of introduction of the protective serum determines the ultimate result of the inoculation; when the serum is injected subcutaneously it is possible that a large proportion of its active material is used up and practically wasted in fortifying or assisting cells which stand in little need of protection; whilst the nerve-cells, participating only in the general distribution of the antirabic substance, do not receive from it sufficient help to enable them to withstand the action of the poison which, as we have seen, appears to be especially mischievous to them. When, on the other hand, the serum is injected into the substance of a large nerve, the protective agent finds its way at once into channels which communicate almost directly with the cerebrospinal lymphatic system; and larger quantities of it come into direct contact with the cells or tissues of the central nervous system. In the case of a subdural injection of the serum the antitoxic material comes primarily and directly into contact with those tissues which stand most in need of its protective action; consequently the best results are obtained. Babes combines the serum treatment with the Pasteurean method, especially in severe cases. One great difficulty about the production of serum for this method of treatment is that, up to the present, it has been found impossible to grow the rabic virus outside the body of an animal; the vaccin material can therefore be obtained only in comparatively small quantities and with the

expenditure of much time, trouble, and money. Moreover, the virus is obtained in such a form that it is difficult, if not impossible, to separate the whole of the active portion of the poison from its ordinary vehicle; whilst, as we are still in ignorance of the exact form of the poison-producing organism, we are not in a position either to isolate the latter or to separate an active vaccinating material by precipitation, filtration, or the use of chemical or microbicidal agents. The serum treatment is still in its infancy, and it is quite possible that in certain cases it may not prove so efficacious in general practice as it has been found to be in experimental work; but, from an experimental point of view, the results are so striking that we are entitled to hope for results as good or almost as good in the treatment of hydrophobia in man.

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CO-EXISTENCE OF INFECTIOUS DISEASES

By F. Foord Caiger, M.D., F.R.C.P.

That two or more infectious diseases are capable of running concurrently in the same individual is not so generally recognised as the frequency of its occurrence would warrant.

Hunter even went so far as to deny the possibility of such co-existence, and to his teaching must doubtless be ascribed the wide currency to which this belief has attained. Murchison in 1859, while reporting cases in point, asserted that the prevalent opinion was opposed to the possibilities of any such co-existence, though he himself was fully alive to the truth (2).

Now it is universally admitted that the convalescent stage of many and various infectious disorders is not infrequently interrupted by the appearance of a second; and it is within the experience of those who are daily concerned in dealing with large numbers of cases of the infectious fevers, to find two such diseases running concurrently, and in exceptional instances three (3) or even four (4).

So far from co-existence being an impossibility, clinical experience would tend to shew that the presence of one disease in the body increases the liability to the infection of another. The susceptibility not only varies in respect to different diseases, but is usually increased in proportion to the severity of the primary attack.

Any inference, drawn from a simple statement of figures, as to the relative susceptibility evinced by the subjects of a particular disease in respect to the development of any particular second, is unfortunately vitiated by the fact that the liability to contract a disease varies with the chances of exposure to its infection. The varying influences of season, local prevalence, relative isolation, the protection conferred by a previous attack, and other factors, must all be discounted in addition to the varying susceptibility seen in connexion with age.

The following list specifies the number of instances amongst 184,227 cases of scarlet fever, diphtheria, and enteric fever received into the Metropolitan Asylums Board Fever Hospitals during the years 1896-1904, in which two or more infective fevers were actually co-existent at the time of the patients' admission (5):—

Scarlet Fever and	Diphtheria	1721	Diphtheria and	Measles	413
,, ,,	Chicken-pox	634	,, ,,	Chicken-pox	192
,, ,,	Measles	503	,, ,,	Whooping-cough	321
,, ,,	Whooping-cough	689	,, ,,	German Measles	19
,, ,,	German Measles	60	,, ,,	Enteric Fever	14
,, ,,	Enteric Fever	29	,, ,,	Mumps	5
,, ,,	Mumps	6	,, ,,	Erysipelas	1

Enteric fever and Whooping-cough	1
Scarlet fever, Chicken-pox, and Whooping-cough	2
Scarlet fever, Measles, and Whooping-cough	3
Diphtheria, Measles, and Whooping-cough	2
Diphtheria, Measles, and Chicken-pox	2
Diphtheria, Chicken-pox, and Whooping-cough	1
Scarlet fever, Diphtheria, Measles, and Whooping-cough	1

It will be seen that amongst these 184,227 attacks, a second disease was actually coexistent in 4421 instances, *i.e.* 2·39 per cent. If, however, instead of those actually co-existent, we consult the records shewing the occurrence of a second disease during the convalescent stage of the primary attack, the number will be found to be considerably larger.

The following table shews the number of instances amongst 184,227 cases of scarlet fever, diphtheria, and enteric fever in which a second infective fever arose during the convalescent stage of the primary one (5):—

Primary Disease.	Secondary Disease.	No. of Cases.	Percentage.
Scarlet Fever (117,707 cases)	Diphtheria . . .	4535	3·85
"	Chicken-pox . . .	3040	2·58
"	Measles	1617	1·37
"	Whooping-cough . .	778	·66
"	German Measles . .	1030	·87
"	Mumps	117	·09
"	Erysipelas . . .	96	·08
"	Enteric Fever . . .	15	·01
Diphtheria (57,187 cases)	Scarlet Fever . . .	2931	5·12
"	Chicken-pox . . .	574	1·00
"	Measles	512	·86
"	Whooping-cough . .	257	·44
"	German Measles . .	69	·10
"	Mumps	3	·00
"	Erysipelas . . .	4	·00
"	Enteric Fever . . .	2	·00
Enteric Fever (9333 cases)	Scarlet Fever . . .	29	·31
"	Diphtheria . . .	33	·35
"	Erysipelas . . .	1	·01

The foregoing record shews that in 15,643 cases, or 8·49 per cent, the convalescent stage was complicated by the appearance of a second disorder.

If the two series be added together we find that amongst 184,227 cases of scarlet fever, diphtheria, and enteric fever, the attack was complicated at one time or another during its progress by the occurrence of another infective disease in 20,064 instances, or 10·8 per cent. In ten instances three separate infections were co-existent, and in one no less than four diseases were present at the same time.

Now, for the reasons above stated, the foregoing numbers cannot be taken as an accurate expression of the proportionate liability to co-existence; yet the figures are not without a certain value. Experience shews that the diseases which most frequently complicate *scarlet fever* are *diphtheria*, *chicken-pox*, and *measles*, and that *whooping-cough* comes next in frequency, especially in very young children.

Although post-scarlatinal diphtheria is a well-recognised condition, much confusion exists at the present time in respect to those cases of *scarlet fever* which are complicated with *diphtheria* during the acute stage. Seeing that in many cases of simple scarlet fever an exudation is found on the fauces, which is not diphtheria, closely as it may simulate it, the mistake is often made of adopting too wide a generalisation, and of referring all "exudation throats" to the same category; thus virtually ignoring the possibility of the co-existence of diphtheria with scarlet fever in the acute stage. In the large majority of cases in which an attack of

diphtheria complicates scarlet fever, it arises during the convalescent stage of the scarlatinal attack; in which case the infective processes are not strictly co-existent. It must also be conceded that by far the greater number of faucial exudations seen during the acute stage of scarlet fever are not examples of co-existent diphtheria, but are dependent upon inflammation of a special character set up by certain micro-organisms, usually, it would seem, streptococci, which are frequently present in the scarlatinal throat. It must be remembered that diphtheria bacilli are not infrequently present in the throats of persons suffering, or convalescent, from scarlet fever, without giving rise to any clinical manifestations: and in the absence of a bacteriological examination there would be nothing in the nature of the case to lead to their presence being suspected. Since the germs are apparently in a latent or vegetative phase, the patient can hardly be said to be suffering from diphtheria, though the presence of Klebs-Löffler bacilli must always be regarded as a potential source of diphtheria, not only to the person harbouring them, but to others.

That *measles* and *chicken-pox* should frequently be found to arise in children suffering from *scarlet fever* is only what might be expected in view of the high degree of infectivity possessed by these disorders; moreover the age-incidence in the three diseases is in close agreement.

There is little doubt that many more instances of co-existent *whooping-cough* would have to be recorded were the age-incidence in the two diseases more equal. The maximum susceptibility to whooping-cough would appear to be during the second, third, and fourth years of life; whereas in scarlet fever the greatest liability is evinced during the fifth and sixth years.

That *scarlet fever* patients are but little prone to *enteric fever* and vice versa, is evinced by the fact that only 73 instances are recorded in 127,040 attacks. This inference, too, is supported by a statement of Murchison, that in the course of twenty-three years' experience at the London Fever Hospital, at a time, too, when all classes of disease were treated in the same wards, and many thousand cases of scarlet fever were admitted, not more than eight instances were recorded in which the scarlet and enteric fevers were co-existent (6). Here, again, the age-incidence in the two diseases being widely different, the relative susceptibility would naturally not be very great. If it were, the similarity in the curves of their seasonal prevalence would doubtless tend to increase the chance of their occasional co-existence.

That *typhus* is capable of existing with *scarlet fever* is attested by Murchison (6). At the present day the opportunity of observing their co-existence must necessarily be rare. The only case which has come under my own notice was that of a boy aged eight, in whom the typhus eruption appeared on the third day of a typical attack of scarlet fever. The severity of the combined attack was too great for the child, and he died on the fifth day after the eruption came out. In this case the typhus was, no doubt, contracted first.

As in the converse instance, but possibly to a less degree, the

diphtheria patient is very liable to take the infection of *scarlet fever*, and this susceptibility is probably as great in the acute stage as it is in later convalescence. That in both diseases the faucial mucous membrane is the part first and mainly affected, strongly suggests that this part is in each case the point at which infection is received. As regards diphtheria modern research and clinical observation have confirmed this view beyond all reasonable doubt; the mucous membrane of the throat, weakened by the scarlatinal inflammation, provides a soil most favourable to the development of the Klebs-Löffler bacillus. Whether the reverse hold good, namely, that a mucous membrane, either at the time, or previously, affected with diphtheria, is thereby rendered more susceptible to the virus of scarlet fever, is not so certain. The rapid spread of scarlet fever amongst the inmates of a diphtheria ward, if once it gain admission, and its preference for the severer cases, are matters of common observation; moreover, the observation that, in many cases of scarlet fever, a sore throat precedes, by a week or more, the symptoms of definite invasion, strongly suggests that this is so.

It is not uncommon for *diphtheria* patients to be attacked with *measles*, *chicken-pox*, or *whooping-cough*, but it is doubtful whether any special susceptibility exists in respect to any of these diseases.

The subjects of *measles*, though they may develop any of the other infectious disorders, evince a special susceptibility to *diphtheria* and *whooping-cough*. The gravity of the former complication is extreme, as in both diseases the respiratory passages are especially affected. In respect to whooping-cough the liability lasts for some weeks after obvious catarrh has ceased. There would, therefore, seem to be a correlated susceptibility in respect to measles and whooping-cough such as appears to exist between scarlet fever and diphtheria.

The actual concurrence of *small-pox* and *scarlet fever* is not very common, although the small-pox convalescent is very liable to take scarlet fever if exposed to its infection. *Erysipelas*, again, arises occasionally in confluent cases.

Now, as concerns any modification of the characters of one disease in virtue of the co-existence within the body of another, it may be stated that there is no evidence to warrant the belief that the incubation-stage of either is interfered with in any particular. Just as the latent period of independent chicken-pox, measles, or small-pox is more constant than it is in independent attacks of scarlet fever, diphtheria, and enteric fever, so it is when either of them occurs as an intercurrent affection during the progress of another disease. A primary vaccination runs precisely the same course in a scarlatinal child as it does in a healthy infant. Arguing from experimental data so far available, there is no prima facie reason to expect the products of one organism to be capable of modifying the development of another in a medium so eminently favourable to growth as is afforded by the human body; unless the poison be present in overwhelming quantity. The restraining influence of certain putrefactive organisms is, however, admitted.

It may then be affirmed generally, that the symptoms of one disease are neither delayed in their appearance, nor mitigated in their severity, by the presence of another; but that the characteristics of each are for the most part well defined, and in some instances even exaggerated. The gravity of the combined manifestation would seem not to vary so much with the severity of the primary attack, which seems to have more effect in determining susceptibility, as with the propinquity in the incidence of the two disorders.

There are, nevertheless, clinical points characterising the conjunction of certain members of the infectious group which are deserving of mention. When *diphtheria* arises during the acute stage of *scarlet fever* the patient's condition is usually very grave, apart from the chance of extension to the larynx. There is a great liability to mistake a non-diphtheritic scarlatinal exudation, or the surface-necrosis (*Scharlach Nekrose* of Henoch) which is sometimes seen on the tonsils in severe cases of scarlet fever, for the state in which both diseases are present. The following points may assist in discriminating the two conditions:—The scarlatinal exudation is usually limited to the tonsils; it is apparently dependent upon the intensity of the associated tonsillitis; the surrounding mucous membrane is usually of an angry red tint, and frequently presents a somewhat dry and sticky appearance; the exudation itself either consists of a thin pellicle, which is easily detached, and commonly disappears in a day or two, or it is represented simply by a necrotic surface on the tonsil. This soon proceeds to ulceration with a greyish-white, woolly-looking surface which may extend both superficially and in depth, and ultimately lead to extensive destruction of the faucial tissues. At all stages of this condition the *Streptococcus pyogenes*, staphylococci, and numerous putrefactive bacteria are usually to be found in abundance; but the Klebs-Löffler bacillus is conspicuous by its absence, whether sought for in the recent exudation, or by careful cultivation in suitable media; and the attack will not be followed by paralysis. In co-existent diphtheria, on the other hand, the exudation more frequently invades the palate, uvula, and the pillars of the fauces; it is usually thicker, especially at the margin, and for a time more adherent; it bears no relation to the intensity of the tonsillitis, and the mucous membrane is often comparatively pale, of a pinkish tint, and usually presents a glairy appearance. The constitutional depression is more profound at an earlier date than is usual in uncomplicated attacks of scarlet fever. The Klebs-Löffler bacillus can be isolated with ease in practically all cases, together with certain pyogenetic bacteria, notably *Streptococcus pyogenes* and *Staphylococcus albus* and *aureus*; moreover, some degree of paralysis is found at a later stage in a large proportion of patients who survive.

The bacteriological test and the occurrence of post-diphtheritic paralysis are, of course, by far the most valuable criteria of the presence of co-existent diphtheria; and I have often found the Klebs-Löffler bacillus in cases in which a definite diagnosis could not have been otherwise obtained. The majority of such cases are fatal; and the reason why

diphtheritic paralysis is not more frequently observed is that the patients usually die before the advent of this sequel.

Diphtheria of convalescence, or *post-scarlatinal diphtheria*, is dealt with in the section devoted to scarlet fever (p. 461).

When scarlet fever arises in a patient who has recently suffered from diphtheria, that is, during the first few weeks of the illness, a recrudescence of diphtheritic membrane frequently occurs, especially in cases treated with antitoxin; although the fauces may have been clear for the previous two or three weeks. The development is interesting as exemplifying a recrudescence of vitality on the part of a microbe in response to a change in its environment. The relapse, however, is rarely characterised by excessive virulence.

When *chicken-pox* complicates the *scarlatinal attack*, either during the eruptive stage or during convalescence, the attacks are on the whole more severe than in the independent disorder. The eruption is usually more copious, and there is possibly a greater tendency to pustulation. In cases in which the eruptions are coincident, the varicella will have been contracted at an earlier date than its fellow.

It is not very common to find *measles* actually co-existent with *scarlet fever*, although either is frequently to be met with during convalescence from the other. In the former case the diagnosis may give rise to some difficulty, as the combined eruption will present some special features of both diseases. The eruption is usually intense, often patchy in distribution, and generally invades the circumoral region. A *mottled* staining remains behind after the rash has faded, often associated with really free desquamation; a combination which is not met with in any single infectious disease. If the eruptions be nearly coincident, the rapid fall of temperature, which in most cases of ordinary measles takes place within forty-eight hours of the appearance of the rash, may be arrested by the longer sustained pyrexia of scarlet fever, and the temperature may thus be quite devoid of its usual characters. Ulcerative stomatitis is very prone to appear in such cases, occasionally running on to definite noma, and there is a marked tendency for the bronchial catarrh to develop into serious lung mischief.

It is curious that the eruption in *post-scarlatinal measles* often appears earlier than in the independent disease. In seventy-eight consecutive cases of measles arising in scarlatinal convalescents the eruption was delayed until after the third day in four instances only. In a large majority it appeared on either the first or second day; and in a considerable number it was the first sign of illness. These were cases of undoubted measles, not of German measles.

Post-scarlatinal measles is apt to be more severe than ordinary measles; the mortality in the series referred to being over 14 per cent.

The appearance during the course of *measles* of a suffocative cough, attended with progressive laryngeal stridor, usually implies the presence

of membrane in the air-passages. This, in some cases at any rate, is true *diphtheria*.

When *measles* is complicated with definite *diphtheria*, either during the eruptive stage or later, the condition is one of extreme danger in view of the constancy with which the latter disease affects the larynx and respiratory tract. It constitutes the most serious combination of any two infectious diseases. The fatality is not only increased in virtue of the malignant type which the disease assumes, but the persistence with which the membrane re-forms, if successfully expelled, renders the case well-nigh hopeless. Tracheotomy alone is very rarely successful, but, when combined with the administration of antitoxin, the results are most encouraging.

When *measles* occurs in a patient who is suffering from *whooping-cough*, the tendency to the development of capillary bronchitis and bronchopneumonia is thereby greatly increased. The fatality, as might be expected, is in inverse proportion to the age of the patient.

It is remarkable that when the course of *whooping-cough* is interrupted by an intercurrent attack of *scarlet fever*, the characteristic "whoop" is often entirely dropped during the febrile stage of the latter affection, but returns when the temperature has again become normal. The same phenomenon is occasionally observed during an intercurrent attack of measles.

A child once came under my care in whom *scarlet fever*, *diphtheria*, *measles*, and *whooping-cough* were all present at the same time, the only one of these diseases in which the diagnosis was doubtful being diphtheria, for the bacteriological test was not applied. In another case the eruptions of *measles* and *chicken-pox* were mingled with the early desquamation of *scarlet fever* in a child who at the time was suffering from *whooping-cough*. In both cases the combined attack was fatal.

In those exceptional cases in which *enteric fever* co-exists with *scarlet fever* the diagnosis is not likely to present much difficulty, unless the symptoms happen to be very ill-defined. In each of three instances under my observation the distinctions of both diseases were clearly apparent, though in two of them the rashes were actually concurrent. They all made a good recovery. One was complicated with cervical adenitis, and in each case characteristic desquamation followed.

Numerous instances have been recorded by different observers in the past in which the presence of "*diphtheritic membranes*" have been observed in the throat during the course of *enteric fever*. In the absence of the bacteriological test the diagnosis of *diphtheria* may in some instances have been but conjectural. Murchison (7), however, reported one case in which albuminuria and pharyngeal paralysis supervened, and at the autopsy there was membrane in the larynx.

The co-existence of *enteric* and *typhus* fevers would not be very likely to occur in this country at the present day. Murchison (7) reported 5 cases in which the diagnosis could hardly be called in question. In two of them, although the typhus supervened during the course of the enteric

attack, the eruptions overlapped each other, and the patients ultimately recovered. In the absence of the typhus rash the elucidation of the condition would, no doubt, be very difficult.

The only other infective fever of which the diagnosis is likely to give rise to any special difficulty when occurring in connexion with *enteric fever* is *mumps*. It should not be forgotten that a symptomatic parotitis is not infrequently met with as a complication of the former disease.

Instances in which the course of one infectious disease has been complicated by the appearance of a second have been recorded by many competent observers during the last fifty or sixty years; and such concurrences may be frequently observed in the wards of any large fever hospital.

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F. F. C.

INTOXICATIONS

FOOD POISONING
GRAIN POISONING
ALCOHOLISM
OPIUM AND OTHER INTOXICANTS
METALLIC AND OTHER POISONS: INCLUDING POISONOUS TRADES

FOOD POISONING

By H. Batty Shaw, M.D., F.R.C.P.

Introduction.—As is well known, some diseases, such as typhoid fever, cholera, and dysentery, may be spread by food infected with the organisms responsible for these diseases.

The discovery by Selmi, Brieger, and others of various toxic substances which can be separated, in a pure crystalline form, by chemical means from decomposing food, is responsible for the widespread belief that ingesta may be poisonous from the presence of certain alkaloidal substances. Various reasons, however, can be adduced to shew that this conception is largely, if not entirely, erroneous. Thus, although certain alkaloidal substances can be separated from decomposing organic matter by the interaction of great heat and strong acids, it does not follow that these bodies existed before the employment of these chemical and physical methods. It is quite true that symptoms have frequently followed so soon after the introduction of poisonous food as to give rise to the belief that some soluble preformed poisons were responsible for the clinical manifestations. A rapid onset of symptoms, however, does not necessarily point to the presence of a chemical agent; indeed there are now many reasons for believing that the poison is of a more complex nature—in short, is a true toxin molecule, in the bacteriological sense of the term. That bacteria are responsible for the poisoning which follows the ingestion of certain food, is probable because they have been identified in a very large proportion of the epidemics of food poisoning that have been bacteriologically investigated. According to one estimate, fully four-fifths of meat-poisoning epidemics have been proved to be due to the ingestion of the flesh of animals suffering from bacterial infection. Out of more than 100 epidemics of food poisoning, affecting more than 6000 people, van Ermengem (21) could find only nine in which the healthiness or the reverse of the animals, from which the meat was derived, was unknown, as against 103 epidemics in which it was known definitely that such animals were suffering from septicæmia, pyæmia, enteritis, and other diseases. It is also conceivable that meat may be contaminated with pathogenetic organisms after the slaughter of the animals. Further, milk and milk-products, as well as meat, may be

poisonous as the result of infection; thus, milk may contain pathogenetic organisms when obtained from the cow, or it may be infected subsequently. The question, however, remains whether food undergoing putrefaction—that is, the changes associated with the production of offensive gases as the result of the activity of putrefactive organisms such as the *Proteus zenkeri*, *Proteus mirabilis*, *Bacillus pyocyaneus fœtidus*, *Micrococcus fœtidus*—is able to produce some of the symptoms of food poisoning.

The ptomaines described by Gautier, Brieger, and others, such as neuridine, saprine, putrescine, methylamine, collidine, although at one time thought to be of importance as toxic agents, are now considered to possess very slight poisonous action. It is not, moreover, agreed that putrefactive organisms or their products are capable of producing symptoms of poisoning in man, for it is argued that the mere production of symptoms experimentally by the intravenous injection of toxins derived from these organisms, does not prove that similar symptoms in epidemics of food poisoning are necessarily due to the same agent.

There are considerable difficulties with respect to the use of the word "saprophyte" as opposed to pathogenetic organism. Nearly all pathogenetic organisms can be cultivated in the laboratory and can live and produce poisons outside the animal body, and are therefore facultative saprophytes. But van Ermengem maintains that certain obligatory saprophytes can form toxins capable of producing pathological effects clinically and experimentally. It is also maintained that certain putrefactive organisms are pathogenetic in the same way, so that when it is remembered that various organisms can grow upon meat, and can produce toxic agents capable, when injected intravenously, of giving rise to symptoms of enteritis in animals, there is some reason to believe that the same toxin, when present in food, may be absorbed from the alimentary tract of human beings, and produce the enteritis of food poisoning. The consumption of venison and game, however, is not usually followed by these symptoms, and there are strong reasons for hesitating to accept the opinion that putrefactive organisms are the cause of food poisoning. The discovery of a putrefactive organism in food does not exclude the possibility that a pathogenetic organism originally present had been outgrown by the possibly harmless putrefactive organisms. Although many of the original ptomaines are now known to be harmless, some, such as choline, which has been found in cholera cultures, have been shewn, in quite another department of medicine, to be capable of producing convulsions. Convulsive seizures are, however, conspicuous by their absence in the records of food poisoning, so that even such a toxic substance as choline cannot have much to do with food poisoning.

In the light of recent research, the subject of food poisoning may be summarised in the following way:—

(1) Food poisoning, in an increasingly large proportion of cases, is due to the action of pathogenetic organisms which are either present

before death in the animal from which such food was obtained, or have subsequently gained access to such food. In both cases the human being may suffer from toxic effects either immediately or only after an interval—the period of incubation. The duration of the incubation will depend upon a number of circumstances, such as the virulence of the organism, the resistance of the individual, and so forth.

(2) Ptomaine poisoning, which was originally held to be responsible for various epidemics of food poisoning, is a very restricted possibility. Decomposed food is rarely an attractive article of diet, and even when game or high cheese is eaten in considerable quantity, toxic symptoms are exceptional or entirely absent. In many cases of food poisoning the food consumed has appeared to be quite free from putrefaction, as tested by the sense of smell. Moreover, it is admitted, by those who believe in ptomaine poisoning, that many ptomaines are much less toxic than the fluids from which they were separated.

(3) It is impossible to deny that a few ptomaines, such as mydaleine and tyrotoxicon, may occur in tainted food before ingestion, or may develop during intestinal decomposition and cause toxic symptoms, referable to local disturbances of the alimentary tract, or in the case of mytilotoxine, of the central nervous system also.

A knowledge of the temperatures necessary to destroy toxins has a very important bearing in the consideration of food poisoning. As will be seen later, exposure of food to a temperature of 60° to 80° C., or even to boiling-point for a period as long as thirty minutes to an hour and a half, is not sufficient to destroy certain toxins. It follows therefore that, despite the greatest care in cooking, safety cannot be assured unless the most searching inspection of meat and food be carried out. Recent researches by Drs. Klein and Durham, and many foreign investigators, shew that a still more rigorous examination is necessary in order to detect with certainty the organisms of meat poisoning. Possibly apathy towards this important safeguard has resulted from the failure of the conception of ptomaine poisoning to carry conviction to toxicologists.

Another problem is whether, in the absence of bacterial invasion, food can undergo any change leading to the production of toxic substances. According to von Jaksch, pure milk kept warm in closed vessels may manufacture substances which are not destroyed by sterilisation. The only agency by which such changes can be brought about in the absence of bacteria, aerobic and anaerobic, is that of the intracellular ferments so widely distributed in animal tissues, and possibly present in milk also. These ferments, acting upon the proteid and nucleo-proteid of the animal cell, produce decomposition-products very similar to those produced by heat, acids, and bacteria. This action is hydrolytic ; water is split up and the free hydrogen and hydroxyl, combining with the constituents of the cell, give rise to the various amino-compounds, hexone-bases, ammonia, and so forth, derived from proteid, and purin derivatives, such as xanthine, hypoxanthine, pyrimidine derivatives and phosphoric acid from the disintegration of nucleo-proteids. These bodies, included

under the old term "leucomaines" by Gautier, are very feebly toxic even on experimental injection; so that the danger of food thus altered is at least doubtful. The symptoms ascribed to the ingestion of purin bodies, such as hypoxanthine, are very different from those following the consumption of food infected with micro-organisms, or permeated with their toxic products. Though it is probable that a diet consisting of large quantities of proteid and nucleo-proteid, when prolonged over many years, is capable of disturbing the balance of health, symptoms of an acute character, comparable to those of ordinary food-poisoning, are not met with. Further, a certain amount of disintegration of proteid and nucleo-proteid is a valuable quality, for meat that has hung for some time is more easily digested, and is more sapid than fresh meat, a change attributed to intracellular ferments. Albumoses and peptones are formed in the initial disintegration of proteids; the intravenous injection of these bodies gives rise to toxic symptoms, such as a fall of blood-pressure. There is, however, little reason to believe that when introduced into the alimentary tract these substances can be absorbed as such, and cause the symptoms met with in food poisoning. They would, in ordinary circumstances, undergo the disintegration common to similar products by the hydrolysis of proteids in natural digestive processes.

In face of the overwhelming evidence in favour of the belief that food poisoning is, in a very large proportion of the cases, due to organisms and their toxins, using the term in the bacteriological sense and viewing with suspicion the conception of ptomaine poisoning, *i.e.* poisoning by chemical substances derived from bacterial organisms or by leucomaines or substances derived from the various chemical processes of the body, the etiology of food poisoning may well be introduced by a consideration of these micro-organisms which have been shewn to be responsible for outbreaks of various forms of food poisoning.

Etiology.—(I.) Meat Poisoning.—(*a*) *Bacillus enteritidis* (Gärtner).—The opinion that food poisoning is due to bacterial agencies was first brought into prominence by Bollinger, who attributed certain alimentary disturbances to mycotic influence, and described the condition produced as "intestinal sepsis" or "septico-pyæmic gastro-enteritis." Dr. Klein (28), one of the first to work at the important subject of food infection, investigated in 1880 its bacterial origin in an epidemic at Welbeck reported on by Dr. Ballard (5), and subsequently demonstrated a short bacillus in the lungs of animals experimentally fed with food (salted pork) that had been proved by Dr. Ballard (6) to be responsible for another epidemic of pleuro-pneumonia at Middlesborough in 1888. It is noteworthy that in this epidemic the disease was transmitted from one person to another, that is to say, a disease originated by infected food spread subsequently like an infectious disease. In the same year, 1888, Gärtner described an organism recovered from some meat known to have produced symptoms of gastro-intestinal disturbance in man. This organism is the well-known *Bacillus enteritidis*, and possesses characters

which place it in a position intermediate between the *B. typhosus* and the *B. coli communis.* It differs from these two organisms in a number of ways, but an important distinction is that its toxin appears to be able to resist heat; it is infective *per os* and entering the system can produce a hæmorrhagic septicæmia. The epidemic investigated by Gärtner affected fifty-eight out of ninety-three persons who had eaten the flesh of an ox which had been killed because it had diarrhœa. One of the affected individuals vomited shortly after taking the food and died in thirty-six hours. Microscopic examination shewed that the capillary blood-vessels of the meat contained numerous bacilli, which by cultural methods were proved to be identical with the bacillus present in the organs of the fatal case. Since Gärtner's discovery numerous investigations have been made on food poisoning, and organisms have been separated which recall the morphological features of the *Bacillus enteritidis* so strongly that it has been presumed that the organisms in all these cases were identical with one another and with this organism.

As will subsequently be seen (*vide* p. 878) there is every reason to believe that there is a considerable number of organisms which, though closely allied morphologically, and even in their pathological results, to the *B. enteritidis*, are really different varieties possessing quite different agglutinative reactions; as was shewn by Dr. Durham, who investigated outbreaks of food poisoning at Hatton (16), Chadderton (15), Surbiton, and Oldham (18), and found that each of these epidemics was due to the infection of food by organisms belonging to the group of the *Bacillus enteritidis*, but differing from this organism in important particulars. But how do the animals from which such infected meat is obtained become infected? They may be infected from food, not necessarily derived from other animals, but from vegetable sources, and possibly infected by air-borne organisms, but this is not proved. The closely allied organisms belonging to the *Bacillus enteritidis* group have been named according to the particular epidemic for which they have been considered responsible. They fall into one or other of two groups according to their agglutinative reaction (van Ermengem). In the first group, exemplified by the *B. enteritidis* discovered by Gärtner in the epidemic at Frankenhausen, are included the organisms separated by van Ermengem at Moorseele and Ghent as well as organisms isolated by de Nobele, Fischer, and others in various epidemics. The second group includes organisms which show different reactions, and the type taken is the bacillus discovered by de Nobele at Aertryke. Van Ermengem includes in this latter group the organisms described by Dr. Durham in the Hatton, Chadderton, Surbiton, and Salford epidemics, as well as the organisms discovered by Gärtner at Posen and by himself at Calmpthout. The bacillus of hog-cholera may also be included in this group. Several organisms similar to the *Bacillus enteritidis* have been found in various animals, some of which have been shewn to be capable of producing disease in man, and such human disease has been transmitted in epidemic form to other persons; the *Bacillus psittacosis* of Nocard, the *Bacillus typhi murium* of Loeffler, and

the organism described as the *B. pseudo-tuberculosis* may also be said to belong to the *Bacillus enteritidis* group. A "paracolon" or "paratyphoid" bacillus (*vide* article "Paratyphoid Fever," Vol. I. p. 1157) presents affinities to the types of *Bacillus enteritidis*, but so far has been associated with only one definite epidemic of meat poisoning. Trautmann has described an epidemic of meat poisoning at Düsseldorf following the consumption of horse-flesh; the organism separated was the bacillus of paratyphoid fever. Mr. H. de R. Morgan has studied the organisms belonging to the meat-poisoning group and the paratyphoid group in their distribution in the intestines of animals such as the horse, bullock, ox, sheep, and pig. He finds that the organisms present in the intestines of these animals fall into one of three groups, according to their agglutinative reactions, namely, a group closely allied to the bacillus responsible for the meat poisoning at Aertryke, a group allied to the *Bacillus psittacosis*, and a group allied to the bacillus of paratyphoid fever (type A of Schottmüller).

Important investigations have been carried out on the toxins of the *Bacillus enteritidis*. Fischer and van Ermengem have found that the *Bacillus enteritidis* possesses an endogenous toxin. Fischer maintains that this toxin is not destroyed by prolonged heat. Dr. Sidney Martin (42) has shewn that, except in its resistance to heat, the toxin of *Bacillus enteritidis* is similar to that obtainable from the *Bacillus coli communis*, and Cathcart has recently confirmed this observation and shewn that the endogenous toxin of this organism, obtained by prolonged autolysis or by grinding up the bacilli by the method of Dr. A. Macfadyen and Mr. Rowland, resists boiling for thirty minutes.

(*b*) *Bacillus Typhosus.*—It is unnecessary here to discuss the infection of meat by the *Bacillus typhosus*, but attention may be drawn to Jacobsthal's observation that the meat taken from a cow with a splenic abscess caused an epidemic of typhoid fever; from the pus of the abscess he recovered organisms which gave an agglutinative reaction identical with that of the typhoid bacillus. Babes (4) also states that the true typhoid bacillus has been found in pork.

(*c*) *Bacillus Botulinus.*—It is well known that in certain countries, especially on the Continent, epidemics of meat poisoning have occurred from time to time characterised by a very definite group of symptoms referable to the nervous system. The food consumed has frequently been in the form of sausages made from liver, blood, and so forth; but similar symptoms have followed the consumption of salted and smoked meat, ham, various forms of game, preserved meat, and pies made from these articles. The name of botulism or allantiasis has been given to this group of symptoms. As in the past other symptoms following the consumption of meat have been attributed to ptomaine poisoning from putrefaction, so a similar explanation has also been given of botulism. It was observed, however, that the organisms of putrefaction are remarkable by their absence or by their rarity in such food, and that the amount of ptomaine that could be extracted was very

small and incapable of producing symptoms of true botulism. Various efforts have been made to discover the organism concerned, but little has resulted beyond the discovery of aerobic bacilli, possessing all the characteristics of the *Bacillus coli communis*.

In the year 1897, however, van Ermengem (20) drew attention to an anaerobic bacillus which he had found in 1895 in some ham, parts of which had been eaten by five people, three of whom died. The animal from which the ham was prepared was evidently free from disease, for another part of its flesh was eaten shortly after slaughter and caused no symptoms; moreover, the second ham prepared from the animal had undergone putrefaction, and yet persons partaking of it did not develop symptoms similar to those of the other persons who had partaken of the first-mentioned ham, and the only organisms separated were the *Bacillus proteus* and the *Bacillus coli communis*. The first-mentioned ham alone produced symptoms of botulism, and it was one which had been submerged in a pickling fluid. From this ham van Ermengem was able to separate an anaerobic sporogenous bacillus, the *Bacillus botulinus*, which, although capable of producing fatal toxins, was, he states, unable to grow in the living body. This is a somewhat remarkable statement, because he reports that he found the bacillus in the spleen of one patient who died, as well as in the spleen of an animal fed with the ham. Van Ermengem considered it not a true pathogenetic organism, but rather a saprophyte capable of producing toxins; his reasons for considering this organism as non-pathogenetic in the ordinary sense need not be discussed at present, but it may be said that Dr. Durham and other observers do not accept van Ermengem's view that the *Bacillus botulinus* is a toxigenous or pathogenetic saprophyte.

To return to van Ermengem's observation, watery extracts of the poisonous ham yielded on filtration a fluid of highly toxic character. Such extract exposed to heat of 80° C. for half an hour, or treated with carbolic acid and exposed for a long time to air and sunlight, shewed a complete loss of toxicity. The toxin of the *Bacillus botulinus* resembles in several ways, especially in its highly poisonous character, the tetanus toxin, and like it is apparently fixed by the cells of the central nervous system. The toxin of the *Bacillus botulinus* when injected subcutaneously in doses of ·0001 to ·0005 c.cm. of a filtered broth culture is fatal to rabbits. An observation of greater importance is that 1 to 2 drops of a broth or gelatin culture administered to guinea-pigs by the mouth causes death in twenty-four to thirty-six hours with pronounced paralytic symptoms. The same results occur in monkeys after administration of the poison by the mouth. Dogs, cats, and fowls are very much less susceptible to the toxin given by mouth, and dogs, even after the subcutaneous injection of 10 to 30 c.cm. of a filtered culture, react only with fever, local suppuration, and wasting. Van Ermengem found that the amount of ptomaines present in the food was exceedingly small.

(*d*) The *Bacillus coli communis* appears to occupy a dual position; sometimes it acts as a putrefactive bacillus, on other occasions it assumes

pathogenetic characteristics. Like putrefactive organisms, it may produce an unpleasant odour in the meat upon which it grows. It may be expected that its presence in meat used for food may give rise in certain cases either to infection or to intoxication.

Dr. Klein (29) in 1889 described an organism closely allied to the *Bacillus coli communis* which was responsible for an outbreak of food poisoning at Carlisle following the consumption of pork and a certain gravy-stock. He investigated a similar epidemic at Portsmouth in 1890 which followed the consumption of meat-pie, and suspected the organism of this epidemic to be the *Bacillus coli communis*, though subsequent inquiry led him to believe that the organism was the *Bacillus enteritidis* (34). Further evidence that *Bacillus coli communis* may infect meat is provided by Dineur (quoted by van Ermengem), who was able to shew that an epidemic of sausage poisoning was due to a highly virulent *Bacillus coli communis* in the food. Fischer also separated a virulent *Bacillus coli communis* from pickled meat and from goose-liver.

(*e*) *Bacillus Proteus.*—As already pointed out, some authorities do not believe that the toxins of putrefactive bacteria produce the symptoms of meat poisoning; for the discovery of a putrefactive organism in food and the demonstration of its toxic effects when injected experimentally into a vein, or subcutaneously, is obviously not sufficient proof that it is the cause of similar symptoms in man occurring after the consumption of food containing the organism; though of course it is somewhat suggestive. Dr. Durham obtained by cultivation from the liver of a patient dead of infection with Gärtner's bacillus, numerous colonies of this bacillus as well as a few of the *Bacillus coli communis.* A sample was kept, and on plating out from it again a few days later, the *Bacillus coli communis* and a few examples of the *Bacillus proteus* were recovered; but there were no representatives of the *Bacillus enteritidis.* A week later fresh plating shewed the *Bacillus proteus* only; the other two organisms seemed to have died out.

However, the notion that organisms of putrefaction can produce toxic symptoms has so impressed other observers that reference must be made to the subject. As the name implies, there are several varieties of the *Bacillus proteus.* Unlike the *Bacillus coli communis,* it does not produce a fæcal odour, though it is associated with the usual putrefactive odours. Salus has recently brought forward reasons for excluding the *Bacillus proteus* from the group of putrefactive organisms, on the ground that this organism is unable to produce putrefaction of fibrin. He is also inclined to follow the teaching of Pasteur, that true putrefactive bacteria are obligatory anaerobes; the *Bacillus proteus* is an aerobic organism. The earlier investigations of Brieger and others were directed to the separation, by chemical and physical means, of derivatives of putrefactive organisms, which included the *Bacillus proteus*; to these substances the term ptomaine was applied.

Various epidemics of meat poisoning through the alleged agency of the *Bacillus proteus* have been described, such as those by Levy, by Dr.

Klein (32) in an epidemic of poisoning by potted meat at Mansfield, by Wesenberg, Schumberg, Glücksmann, and Silberschmidt.

Dr. Sidney Martin (47) has shewn that it is possible to demonstrate in the filtered cultures of the *Bacillus proteus*, and in the bodies of these organisms, a toxic substance closely combined with a proteid which is not an albumose. This substance is readily extracted from the dead bodies of the bacilli by distilled water. He also observed that this toxin when injected intravenously into rabbits causes a fall of temperature even to an extreme degree, rapid evacuation of the intestinal contents, great bodily weakness, vomiting, and even death. Exposure to a temperature of 100° C. for a short time does not destroy the toxin. Levy considers that *B. proteus* produces "sepsine," a base described by Schmiedeberg and Bergmann, intravenous injection of which sets up gastro-intestinal symptoms in dogs.

Various other organisms have been discovered in meat, and have been regarded as possible causes of meat poisoning. Dr. Klein (37) has separated from an infusion of beef which was allowed to putrefy, an obligatory anaerobic bacillus which was motile and sporogenous; when injected into guinea-pigs, this organism, described as *B. carnis*, produced death in twenty-four hours.

The particular kinds of meat which are liable to infection are pork, veal, beef, and horse-flesh. As a rule, mutton does not cause meat poisoning, though cases of poisoning from lamb have been recorded by Babes (4) and Zalplachta.

These considerations about infection and intoxication in meat poisoning must raise many questions, especially the possibility that such infections and intoxications may explain certain acute illnesses of doubtful origin. It is known that certain typhoid-like disorders are due to a special paratyphoid organism, and it is conceivable that meat or food infection may be responsible for the numerous cases of zymotic diarrhœa, of various hæmorrhagic disorders, acute bronchial and pulmonary affections, myelitis, various forms of febrile jaundice, and a large group of cases for which at present we have no explanation and can merely label cryptogenetic infection.

As Babes points out, the application of serum-diagnosis to such cases may in the future shew that some at least are due to food infection, not only by typhoid bacilli, but by the paratyphoid bacillus or by that large group of organisms which are generically known as the organisms of meat infection.

Scurvy has been attributed to the want of certain ingredients found only in fresh vegetables. It has, however, been found that scurvy does not develop so long as fresh meat is consumed, and Mr. Jackson and Dr. Harley, by feeding animals with slightly tainted meat, have produced experimentally a disease analogous to scurvy, which was not prevented by giving sound maize and rice at the same time. Torup indeed has suggested that scurvy is due to ptomaine poisoning, but in the absence of bacteriological investigation in Mr. Jackson and

Dr. Harley's research, it is possible that human scurvy is due to the presence of bacteria and to the development of bacterial toxins in the meat consumed.

It is stated that the flesh of animals that have undergone great fatigue just before death is toxic. Richardière suggests that this may be due to the presence of an excessive amount of leucomaines, but Roger conjectures that these animals have really undergone an auto-infection, and Wurtz, supporting the same opinion, quotes Charrin's experiments shewing that fatigue favours the escape of micro-organisms from the intestinal tract into the blood. It is known that the flesh of fatigued animals putrefies much more quickly than that of unfatigued ones.

(II.) Poisoning by Milk and Milk Derivatives.—Milk may become infected by organisms present in the animal from which it is obtained, or by organisms after its removal and before consumption, and in this way may spread diseases, such as tuberculosis, enteric fever, and probably those zymotic diseases which affect children more especially in the summer months and are due to organisms allied to the *Bacillus dysenteriae* (Shiga). It is possible that putrefactive changes occurring in milk may also be responsible for the symptoms produced. Dr. Klein (36) has shewn that pathogenetic varieties of the *Bacillus coli communis* may occur in ice-cream. Cultures of this organism, when inoculated in small doses into rodents, produced general hæmorrhagic septicæmia, gastro-enteritis, peritonitis, and death within twenty-four to forty-eight hours. The organism had been recovered from ice-cream responsible for an outbreak of gastro-enteritis in man. This organism was not the *Bacillus enteritidis*, and was not the *Bacillus coli communis*, though it closely resembled it. Dr. Klein (31) has also detected the anaerobic *Bacillus enteritidis sporogenes* in eight out of ten samples of milk subjected to examination; its pathogenicity to rodents was, however, variable. He also found it in the stools in infantile diarrhœa and cholera nostras, and Dr. Andrewes has described epidemics apparently due to this organism.

Out of thirty-nine samples of milk from different counties in this country, Dr. Klein (34) found that ten, *i.e.* 25·5 per cent, contained the *Bacillus enteritidis* (Gärtner); and he points out that in warm weather the organism would have rapidly increased in number without altering the appearance of the milk, and so in the absence of sterilisation of the milk this organism would have been readily capable of producing infection of the individual who consumed the milk. As already pointed out the toxin of the *Bacillus enteritidis* is not destroyed by heating for a considerable time to 100° C., so that ordinary methods of sterilisation would not have rendered such milk harmless.

Drs. Darra Mair and W. H. Brook have described an epidemic occurring in Lincoln which simulated, but was in reality quite distinct from, scarlet fever. This epidemic, apparently due to milk infection, affected forty-three people, and caused the death of one from septic phlebitis, hemiplegia, and coma. Drs. Klein and Gordon have brought forward evidence to shew that this epidemic was due to a yeast closely related to

Oidium albicans, though not identical with it, and they have given it the name of *Saccharomyces hominis*. The yeast was obtained by culture from three swabs out of the seventeen submitted to examination.

Poisoning by cheese has attracted much attention since the remarkable outbreak in Michigan, in 1883-4, of an epidemic which was investigated by Vaughan. He was able to separate, by means of extraction by ether of an alkaline watery extract of the cheese, a crystallisable substance to which he applied the name tyrotoxicon—a term previously used to describe a poisonous substance suspected to be in cheese, but not separated in a pure state. Tyrotoxicon has also been found in milk, ice-cream, and custards. Vaughan considered it to be the result of putrefactive changes in the food, but has not been able to discover the organism. Tyrotoxicon is, however, a comparatively rare poison in cheese; and in 1890 Vaughan, having failed to obtain evidence of its presence in several cheeses known to be poisonous, carried out further investigations which led him and his collaborators to conclude that in certain cheeses a bacillus occurs which belongs to the colon group and contains an intracellular toxin. He found that this toxin is not destroyed by such extreme heat as 184° C., and is capable of exerting pathological effects when injected into guinea-pigs. Obviously this organism is not the *Bacillus coli communis*, for the toxin of this organism is destructible at much lower degrees of temperature. Possibly the organism discovered by Vaughan really belongs to the meat-poisoning group of organisms. Lochte points out that some cases of cheese poisoning are due to infection with an organism allied to the colon bacillus, and considers that in the remainder the symptoms are probably due to intoxication by the products of this organism. Even butter has been found to produce symptoms allied to milk and meat poisoning, and presumably similar organisms are responsible for such effects. It is probable that in poisoning by milk and milk-derivatives, bacteria are responsible for the symptoms either directly or indirectly through the influence of their toxins, and that, as in meat poisoning, hesitation to accept this origin of food poisoning has been caused by our ignorance of the resistance to heat of the various toxins concerned.

(III.) Poisoning by Fish.—What has been said about milk and milk derivatives applies equally well to fish. The name of ichthyotoxismus has been given to the symptoms produced by poisonous fish. According to Ulrich, fish poisoning may be due to the infection of living fish, such as sturgeon, carp, or barbel, by the *Bacillus proteus*, or the food may be infected after the death of the fish and before it is eaten. Probably the epidemic of malignant œdema described by Sir T. Stevenson was due to microbic infection of sardines in this way. In some cases fish have produced toxic symptoms, and the organism recovered from the food has been recognised as the *Bacillus paratyphosus*, variety B, described by Schottmüller; Stoll described an epidemic in which two families were affected; seven people fell ill, and two died. Schottmüller's organism was recognised by Silberschmidt. Other cases of fish poisoning have

been ascribed to the *Bacillus botulinus*. Salted cod occasionally becomes red in colour, and is then found to be very toxic. At one time it was thought that this was due to a chromogenetic fungus, but Wurtz states that the toxicity is due to the action of bacteria which flourish more abundantly in the presence of other chromogenetic fungi.

Another form of fish poisoning, however, depends upon quite different factors. The roes of certain fish are more poisonous at the spawning seasons than at others. This is well known in the case of the sardines caught in the Antilles, in the case of the tunny fish, or Spanish mackerel, in the case of the pike, and especially of the barbel. The consumption of the ovary of the barbel gives rise to a group of symptoms simulating those of cholera, hence the German term of Barbencholera. Sometimes the muscle of fish is made harmful by admixture with poisonous organs derived from the same animal; for example, various species of tetrodon found in the Japanese and Chinese seas, in the East Indian Archipelago, and at the Cape, are especially poisonous if the flesh be contaminated with the liver, stomach, or ovary; a curari-like substance, fugin, is said to be responsible for this effect. Günther has shewn that certain members of the herring tribe, which ordinarily possess neither poisonous flesh nor poisonous organs, become harmful when they feed on certain coral banks. Fatal gastro-enteritis has been known to follow the consumption of such fish in these circumstances. *Petromyzon fluviatilis*, the lamprey or "Nine-Eyes," in the fresh condition, or even after washing or boiling, causes symptoms of poisoning; but, if first treated with salt, the animal discharges a large amount of mucus and becomes innocuous (Kobert).

Shell-fish.—Very considerable interest attaches to the study of bacterial infection following the consumption of certain crustaceans, molluscs, etc. Symptoms of poisoning are known after eating lobsters, shrimps, crabs, periwinkles, and edible snails. Oysters, too, have been considered to be the vehicle of typhoid and allied diseases, and no consideration of food infection would be complete without a reference to the grave danger of mussel poisoning. It is stated that the health of mussels can be materially affected by unhealthy surroundings, such as sewage discharge; and it has been stated that the disturbance of its health thus induced leads to the accumulation within the liver of the mussel of certain products of disturbed metabolism. It was formerly supposed that the poison of mussels was of purely putrefactive origin; but this opinion, and the one which attributed the symptoms to copper poisoning are no longer held. It must be admitted, however, in the light of recent researches on other forms of food poisoning, that the explanation that mussel poisoning is due to metabolites produced in the mussel as the result of unhealthy surroundings, is equally unsatisfactory; the whole subject requires thorough re-investigation. Our present knowledge dates from an epidemic of mussel poisoning at Wilhelmshaven, reported on by Virchow in 1885, in which an alkaloid mytilotoxine was separated. E. Salkowski found that the toxicity of the mussels

was due to an organic substance soluble in alcohol; 5·5 mgm. of the dried residue of the alcoholic extract sufficed to kill a rabbit of 1 kilogramme in much the same way as curari does. Brieger separated this substance, and gave it the formula of $C_6H_{15}NO_2$. Wolff found that the toxic substance was mainly accumulated in the liver. Since it was possible to render the mussels quite harmless by exposure to fresh sea-water, and to make them poisonous again by replacing them in the harbour water, it is highly probable that the formation of mytilotoxine is due to bacteria. As the *Bacillus botulinus* is the most common cause of so-called ichthyotoxismus, it has been suggested that mussel poisoning is also due to this micro-organism; but, as will be seen in the section on Diagnosis, there are strong clinical reasons against this. Ostertag concludes that mussel poisoning must be considered an intoxication *sui generis*.

(IV.) Vegetable Poisoning.—Reference to poisoning by vegetable products, as in the case of ergotism or pellagra, will be found elsewhere. It is obvious that tinned meats and tinned fruits may contain poisons of an inorganic nature derived from the metal covers enclosing them. [*Vide* "Metallic Poisoning."]

Potato Poisoning.—In various plants belonging to the *Solanaceæ* there occur, in certain circumstances, two glucosidal alkaloids—solanin and solanein. Solanin is very similar in action to saponin, and occurs in cabbages and green fruits, and in the jackets and "eyes" of potatoes, especially in those which are beginning to grow. Fowls and other domestic animals are said to have been poisoned by these parts of the plants, and by the water in which potatoes have been cooked. Although apparently characteristic symptoms occur in domestic animals, such as paralysis and dilatation of the pupil, there are comparatively few reports of potato poisoning in man, and in these the symptoms have been mainly those of gastric irritation. Pfuhl described an epidemic of poisoning, affecting fifty-six soldiers belonging to a German regiment, due to potatoes that had begun to sprout. Schmiedeberg and Meyer have suggested that potato poisoning is also due to the action of bacteria, whereby the amount of the solanin present, normally ·064 gramme per kilogramme, is increased when the potatoes sprout or are grown only partially covered with earth. Weil found that the percentage of solanin is increased by the action of at least two of the thirteen bacteria he investigated—the *Bacterium solaniferum noncolorabile* and the *Bacterium solaniferum colorabile*—whereas the remaining eleven organisms failed to produce any increase in the amount of solanin.

Landmann has reported an epidemic of food poisoning following the use of bean-salad. Twenty-one people were affected and eleven died. The symptoms produced were remarkable, and suggested the action of a nerve poison resembling that produced by the *Bacillus botulinus*. Indeed, Landmann was able to separate the *B. botulinus* from the fragments of meat which had been incorporated in the salad. Dieudonné has also described an epidemic of potato poisoning in which the *Bacillus proteus* was recovered.

It is not easy at the present moment to say whether solanin poisoning is a reality or not. There are some reasons to believe that bacilli other than those which lead to an increase of solanin are responsible, even for this form of food poisoning; Dieudonné found that the amount of solanin present in the suspected potatoes was only ·012 gramme per kilogramme, or less than is usually found in harmless potatoes, and yet the symptoms agreed with those usually ascribed to solanin poisoning.

Vegetable products have been shewn to harbour the *Bacillus coli communis* by Drs. Klein and Houston, who were able to demonstrate it in wheat, flour, oats, rice, and oatmeal purchased at random at various establishments.

Mushroom Poisoning. — The symptoms of mushroom poisoning, or mycetismus, have been variably ascribed to idiosyncrasy, to the accidental ingestion of inedible varieties containing intrinsic poisons such as *phallin* and various other toxic substances, and to the development in the fungi after gathering and in a variety of circumstances, such as putrefaction, of such alkaloidal bodies as muscarine. These etiological possibilities seem at first sight reasonable and adequate; but a study of the symptoms produced by the experimental introduction of the various active principles which have been separated, and a comparison of them with the symptoms found in mushroom poisoning, shew that our knowledge of the etiology of mushroom poisoning is unsatisfactory. Nor is the influence of putrefactive and other organisms well understood, and little attention has been paid to the possible influence of autolysis in the genesis of harmful agencies, quite apart from mycotic influence and the existence of natural intrinsic poisons. Mr. Worthington G. Smith states that it is believed that some mushrooms are harmful by virtue of other parasitic fungi which produce changes in the host; thus the common edible fungus is sometimes attacked by the *Mycogona alba.*

It is impossible to avoid the suggestion that possibly in all cases of mushroom poisoning, even in those in which symptoms are said to have arisen as a result of putrefactive changes, the genuine cause of the toxic symptoms is the accidental inclusion of some poisonous fungus. It is remarkable that cases of mushroom poisoning are not more common even in this country than they are, considering the very real difficulty that must be met with in distinguishing poisonous from edible varieties, and the very toxic nature of some common varieties of harmful mushrooms.

[Table

COMMON VARIETIES AND CHARACTERS OF BRITISH FUNGI.

Name.	Synonym.	Poisonous or Edible.	Pileus or Cap.	Lamellæ or Gills.	Spores.	Stipes or Stalk.	Annulus or Ring on Stalk.	Volva or Cup at Base of Stalk.	Habitat, etc.
Agaricus campestris.	Psalliota campestris, Agaricus edulis.	Edible.	White or whitish-brown.	Whitish salmon colour, pink, purple-brown, and even black; never clay-coloured or brown.	Dark purple-brown.	Nearly cylindrical; solid.	Yes.	No.	Open pastures; very rarely near trees. Ag. arvensis, horse- or meadow-mushroom, may possibly be a large and coarse variety of Ag. campestris; it is the common market mushroom obtained from the fields, and grows especially on manured soils, even near trees or bushes.
Marasmius oreades.	"Fairy ring" champignons.	Edible.	Small pale buff cap with darker disc.	Whitish.	White.	Solid and stiff.	No.	No.	Open pastures and lawns; easily recognised by its growth in "fairy rings."
Agaricus phalloides.	Amanita phalloides.	Poisonous.	Cap is white, pale yellow, or pale green; and may have on its upper surface "warts," which are remnants of the volva which formerly covered it.	White.	White.	White; bulbous and hollow; and encased in a cup or volva, which may be out of sight, buried in soil or dead leaves.	Yes.	Yes.	Grows very commonly in woods, especially near oak trees; not in pastures; has a penetrating offensive odour.
Agaricus muscarius.	Amanita muscaria, fly-mushroom.	Poisonous.	Scarlet, crimson, yellow or brown cap; with white or buff fragments of the volva on the upper surface.	Pale sulphur yellow.	White.	Stalk hollow; bulbous.	Yes.	Yes, closely applied to the stalk.	Common in woods near birch trees.
Boletus edulis.	The "cep" of the Continent.	Edible.	Light brown cap; sometimes greyish-brown or chestnut.	No gills on the under surface, but numerous tubules with small openings; and on surface is at first white, then greenish-yellow.	Yellow-brown.	Stalk stout and swollen, and pale brown in colour.	No.	No.	Common in woods, especially beech.
Morchella esculenta.	True morel.	All known species are edible.	Cap is globular, oval, or conical, and resembles a mass of honey-comb; colour, tawny or smoky brown.	No gills.	Whitish.	Stalk smooth or broadly furrowed; of variable colour.	No.	No.	Hedges and bushy places, or near ash and elm trees.
Helvella crispa.	False morel.	Edible.	Cap twisted; only as thick as brown paper; pale brown.	No gills.	Spores in asci on upper surface white.	Stalk white, fluted, and irregular.	No.	No.	In woods and damp grassy roadsides near hedges; Helvella esculenta of Continental writers is poisonous when fresh.
Tuber æstivum.	British truffle.	Edible.	Hard black warty spheres as big as walnuts.	No gills.	Large oval spores nearly black.	None.	No.	No.	Grows underground in copses or plantations of beech, oak, or birch.

Mr. Worthington G. Smith states that no reliance can be placed on the colour of the gills as a means of separating the poisonous from the edible varieties. It is more important, even essential, to observe the colour of the spores; frequently the colour of these is the same as that of the gills, but while the colour of the spores is constant, that of the gills varies during the growth. In order to discover the colour of the spores, he recommends that the cap or pileus of the mushrooms, which are being examined with the object of distinguishing the *Agaricus campestris* or *Agaricus arvensis* from the *Agaricus phalloides* or *Agaricus muscarius*, after removal from the stalk, should be placed on a piece of paper or glass with the gills lowermost; in a few hours the spores will have fallen off and have formed a coloured pattern of the gills; the white spores of the poisonous varieties form a marked contrast to the coloured spores of the edible fungi. *Marasmius oreades* is readily distinguished by its habit of growing in the familiar "fairy rings," and the Boletus, Morchella, Helvella, and truffle are readily distinguished by their respective peculiarities above indicated. It is recommended to scrape away the tubes on the under surface of the Boletus before cooking. The British truffle is not much in favour as an article of food, the French representative, *Tuber melanosporum*, being preferred. It is universally agreed that it is quite useless to depend on the popular methods of distinguishing harmless from poisonous mushrooms; appeal must be made to the botanical characters. The blackening of articles of silver placed in mushrooms which are being cooked is no test of their harmfulness; nor can poisonous mushrooms be rendered innocuous by macerating in cold water, except in the case of *Agaricus muscarius*, or by adding salt, vinegar, or tannin. Ponfick, Bostroem, Böhm and Külz have shewn that *Helvella esculenta* when fresh contains a poisonous principle, but that washing in hot water, cooking, or even drying renders it innocuous. Most mushrooms, the morel in particular, become very dangerous as soon as they begin to putrefy.

Toxic Principles of Mushrooms.—*Muscarine.*—This alkaloid was discovered by Schmiedeberg and Koppe in *Agaricus muscarius*; choline also was found, and amanitine has likewise been separated from the various amanitæ, and, according to Kobert, is identical with choline. Another alkaloidal body, muscaridine, was separated by Schmiedeberg; but this is identical with pilz- or fungus-atropine, which had previously been described by Kobert. Muscarine is also separable from other fungi, such as the *Agaricus pantherinus*, *Boletus luridus*, *B. satanas*, *Russula emetica*, and *Agaricus phalloides*. Considerable interest centres around the effects produced by poisoning by muscarine as compared with those of poisoning by *Agaricus muscarius*. There are strong reasons for believing that the poisonous effects met with in poisoning by *Agaricus muscarius* are not due to muscarine, or at most in part only; the experimental effects of muscarine poisoning and poisoning by *Agaricus muscarius* are not identical. It is generally believed that *Agaricus muscarius* contains other toxic principles which are responsible for the symptoms produced, and that muscarine does

not exist as an intrinsic preformed poison, but results from the decomposition of neurine, which is derived from the lecithin present so universally in vegetable life. A further difficulty is that muscarine obtained from *Agaricus muscarius* does not produce effects identical with the muscarine derived by chemical means from neurine or choline. According to Harmsen, the substance described by him as fungus-toxin is responsible for some at least of the more characteristic features of mushroom poisoning, especially the symptoms which suggest alcoholic intoxication. Fungus-atropine or muscaridine has also been supposed to neutralise some of the effects from the action of muscarine, so that symptoms of muscarine poisoning only arise when such neutralisation is inefficient.

In men, subcutaneous injection of muscarine in small doses produces profuse salivation, rapidity without subsequent slowing of the pulse, redness of the face, giddiness, anxiety, and, according to some authors, contraction of the pupil, or, according to others, dilatation. All observers agree that disturbance of vision occurs, especially paralysis of accommodation. Perspiration of the face and slightly of the body is also noticeable. After large doses there is slowing of the pulse, vomiting, diarrhœa, convulsions, and death from cessation of the heart-beats.

In contrast with these effects, poisoning by mushrooms, such as the *Agaricus muscarius*, produces intoxication with all the initial signs of excitement, including dilatation of the pupil. Salivation, vomiting, diarrhœa, and slowing of the pulse may be entirely absent. Kobert states that this is more particularly the case with the Fly-fungus obtained from Kamschatka and Siberia, where the natives use the fungus as an intoxicant. The *Agaricus muscarius* of Europe, however, produces symptoms more like those of muscarine poisoning—delirium, dilatation of the pupil, slow pulse, diarrhœa, and vomiting.

Phallin.—Kobert extracted from *Agaricus phalloides* a toxalbumin which he called phallin. This substance is capable experimentally of exerting a marked hæmolytic action. Ford has shewn that, besides phallin, *Agaricus phalloides* contains another active substance which he calls amanito-toxin. Unlike phallin, amanito-toxin is thermostabile, and resists digestion by pepsin and pancreatin. According to Ford, an experimental injection of phallin is followed by subcutaneous œdema and hæmoglobinuria; and, as a result of its blood-laking power, gives rise to pigmentation of the spleen, while amanito-toxin produces hæmorrhages and fatty degeneration of various organs.

Helvellic Acid.—As already mentioned, the toxic effects produced by the consumption of fresh Helvella are due to this body; when dried, this fungus becomes harmless from evaporation of the acid, but it must be remembered that drying does not render other poisonous fungi, such as *Agaricus phalloides* and *Agaricus muscarius*, harmless; muscarine does not evaporate, and is necessarily still present in these fungi after the process of drying. Helvellic acid and extracts of the Helvella produce nausea, vomiting, hæmoglobinuria, icterus, suppression of urine (rarely),

and uræmia. Moreover, cerebral disturbances may also occur, recalling the effects of poisoning by *Agaricus phalloides* and *Agaricus muscarius.*

Other toxic substances have been separated by various workers from mushrooms, but the three mentioned above are the most important. It will be seen that there is still considerable room for a sharper differentiation of the various toxic principles, and of their toxic effects; the importance and real significance of these observations must be accepted with reserve, for the various toxic substances described do not appear to be present constantly in the various fungi in which they were originally detected. This discrepancy harmonises with the considerable variability in the toxic effects of mushroom poisoning in man. Kobert in the last edition of his work admits with disappointment that he no longer believes phallin to be a constant or even frequent constituent of *Agaricus phalloides.*

Pathological Anatomy.—In poisoning by foods such as meat, fish, milk, and the derivatives of milk, containing organisms belonging to the "enteritidis" group, the morbid changes are mainly confined to the alimentary tract and resemble those in severe gastro-enteritis. They are restricted mostly to the small intestines, which are swollen and hyperæmic; the swelling being particularly marked in the solitary follicles and Peyer's patches. The liver may shew hyperæmia, the spleen enlargement, and the kidneys congestion or inflammation. The animals from which the harmful meat was obtained, such as cattle, calves, pigs, may have manifested signs of septicæmia depending upon injury, puerperal infection, and there may be evidence of inflammation of the uterus, joints, umbilical vein; or it may be that they suffered from enteritis and pulmonary inflammation. After slaughter the various members of the *Bacillus enteritidis* group have been found in the spleen, liver, glands, lungs, muscles, and other parts of the animals, so that the use of these particular organs as food is especially apt to be followed by epidemics of food poisoning.

The lesions produced in man by the toxins of the *Bacillus botulinus* chiefly affect the central nervous system and the salivary glands. Marinesco has demonstrated changes in the anterior horns of the grey matter of the cord and medulla, especially of the nuclei of the cerebral motor nerves—oculo-motor, hypoglossal, glosso-pharyngeal, and vagus. Most of the organs shew a certain amount of hyperæmia, with small hæmorrhages and round-celled infiltration. Pneumonia or congestion of the lungs has been a feature in certain epidemics of meat poisoning, for example, the Middlesborough outbreak of epidemic pneumonia. Occasionally mussel poisoning is associated with gastro-intestinal disturbance, and then the stomach and intestines shew the ordinary signs of catarrh.

There may be little or nothing discoverable after death in *mushroom poisoning*, possibly because death has resulted from the effects on the various vital centres of such a toxin as fungus-atropine. When gastro-intestinal symptoms have been well marked, hæmorrhages into, and erosions of, the mucous membrane of the stomach and intestine are

frequently met with. The post-mortem changes seen after poisoning by *Agaricus muscarius* are closely allied to those found in phosphorus poisoning, as shewn by marked fatty change in the liver, heart, and kidney. Ford shewed that similar changes followed the injection experimentally of amanito-toxin. So close is the resemblance to phosphorus poisoning that confusion is very possible.

Symptoms.—The manifestations of food poisoning naturally depend upon the nature of the bacillus or toxic agent ingested; disturbance of the alimentary tract is most frequently observed.

The period of incubation varies considerably in different epidemics of food poisoning. In the present state of knowledge of the various epidemics it is impossible to define sharply the length of the incubation following the ingestion of various organisms. All that can be said is that in the different epidemics the period has varied from one or two to eighteen or thirty hours, and even longer. When symptoms arise immediately after the ingestion of the food the probabilities are that the toxin has been preformed in the food, for example, in authentic cases of meat poisoning due to the *Bacillus enteritidis.* In botulism the onset of symptoms is preceded by a somewhat long interval, viz. twenty-four to thirty-six hours.

The Symptoms of Food Poisoning by Organisms belonging to the Group of Bacillus Enteritidis.—After a varying incubation-period symptoms arise which recall the well-known features of cholera nostras, cholerine, infective diarrhœa, of catarrhal gastro-enteritis, and in some cases of typhoid fever. The onset of symptoms is quite sudden; vomiting may occur, giddiness, diarrhœa accompanied by the passage of yellow or blood-stained offensive motions and great thirst. Sometimes the onset is shewn by a rigor, faintness, muscular weakness, and colicky pains. The temperature may be raised and the pulse frequent and of low tension. Muscular twitching and dilatation of pupils, disturbance of vision and drowsiness may be present and give the case the aspect of the so-called "typhoid" state. Albuminuria and suppression of urine occur, as well as roseolar, erythematous, herpetic, or urticarial skin eruptions. Convalescence may be tedious, and delayed by relapses. In some cases scurvy is simulated, and widespread petechiæ occur. The various skin eruptions may be followed by extensive desquamation, most severe on the palms and soles. As already stated, pneumonia may follow the consumption of meat infected with these organisms.

Symptoms arising from Poisoning by Putrefactive Organisms.—Although decomposed meat, such as game and venison, may be eaten with impunity in moderate amounts, consumption of an excessive amount of such food is occasionally followed by vomiting, diarrhœa, colic, fever, general weakness, and cutaneous eruptions. These symptoms, however, are not so marked as in poisoning by members of the *Bacillus enteritidis* group.

The symptoms set up by changes in food due to the action of the *Bacillus proteus* may appear twelve hours after the ingestion of

the food. Schumburg described an epidemic of poisoning by the *Bacillus proteus* affecting thirty-four people out of a total of one hundred who had partaken of infected beef sausages. The main symptoms were nausea, profuse diarrhœa, and drowsiness. There were no other symptoms specially referable to disturbance of the nervous system.

Symptoms of poisoning by the toxin of Bacillus botulinus may be so characteristic as to make a clinical diagnosis comparatively simple; but this does not always hold good, for on some occasions the symptoms are accompanied by those of gastro-enteritis, so that some other form of meat infection or other disease may be suspected. Van Ermengem states that the symptoms of true botulism, that is to say, those resulting not merely from poisoning by sausages, but by any form of food infected with the *Bacillus botulinus*, are easily recognised. Diarrhœa and vomiting are usually absent, or are only slight and transitory, while obstinate constipation and retention of urine are prominent features. Usually there is no fever and no disturbance of consciousness. The characteristic signs are referable to disturbances of the central nervous system and of the various secretory glands, the former shewn by partial paralysis of muscles supplied by the cranial nerves, resulting in double vision, ptosis, dilatation of the pupils, and paralysis of accommodation, the latter by dryness and redness of the mouth and pharynx; aphonia and dysphagia are also characteristic features. Death results from involvement of the medullary centres.

The symptoms of poisoning by milk, cheese, and other of its derivatives are in the majority of cases gastro-intestinal, and it is probable that in the epidemics occurring after the use of milk and milk products, the cause is, as already explained, some organism allied to the group of *B. coli communis*, *B. enteritidis*, etc.

In some cases the nervous symptoms suggest atropine poisoning—for example, dilatation of the pupils. Double vision, delirium, and lock-jaw also occur, symptoms which were ascribed by von Anrep and others to the effects of ptomatropine, an alkaloidal body which has been found in many other foods, such as meat sausages that have undergone putrefaction. We are quite ignorant of the special organism concerned in the development of this poison, but it is more than probable that a true bacterial toxin is responsible for the symptoms.

The incubation-period of the symptoms in the Lincoln epidemic of milk poisoning (*vide* p. 864) amounted to twenty-four to thirty-six hours. A special feature was intense sore throat with great œdema of the uvula, and the formation of a pseudo-membrane on the tonsils. There was considerable elevation of temperature, but the pulse-rate was not much altered. The tongue was furred, and an eruption occurred in 29 cases, twenty-four to thirty-six hours after the onset of other symptoms. The rash resembled German measles, and was often accompanied by much itching. It generally appeared first on the neck and chest, but occasionally on the face; desquamation followed the disappearance of the rash. Additional features were considerable tenderness and swelling of the cervical glands, stiffness of the

muscles of the neck, signs of gastric disturbance, and pains in the joints. Recovery was the rule, and took place in about a week.

Professor Kenwood and Dr. Vincent have referred to a similar outbreak of illness affecting 500 people, apparently due to milk. Besides malaise, they also noticed very marked affection of the tonsils and cervical glands, as well as high fever, headache, abdominal pains, vomiting, hæmorrhagic stools, and a measly rash. The bacterial investigation of the suspected milk gave negative results. The occurrence of sore throat, rashes, etc., has been noted by other observers amongst the inmates of poor-law institutions, and the symptoms have been variously attributed to bacterial or other infection of milk, or to the presence of preservatives. Dr. Monckton Copeman has described "an epidemic skin disease" with a death-rate of 10 per cent, which was possibly due to the action of preservatives; for in some cases observed, direct bacterial infection could be excluded because, as in the Hendon cases, the amount of preservative present in the milk would have prevented the growth of any organisms. The presence of toxins may, however, explain such an epidemic.

Symptoms of Mussel Poisoning.—Vaughan and Novy have grouped the symptoms of mussel poisoning under three heads. In the first group symptoms indicate simple gastro-enteritis. In the second group these symptoms are exaggerated, and the clinical picture is that of cholera. In the third group the symptoms are referable to the nervous system, and include a sensation of heat and itching, dyspnœa, lividity of the face, and paralysis; coma and death may result. On other occasions such symptoms as nausea, vomiting, various paræsthesias, muscular feebleness, suppression of urine, dilated and insensitive pupils, have been observed. Fever is usually absent. The symptoms may appear soon after eating the food, or be delayed several hours. Brieger states that death may follow in one and three-quarter hours; five to six mussels are sufficient to cause poisoning in an adult.

Symptoms of Poisoning by Fish.—The use of the term ichthyotoxismus is futile, as the symptoms appear to be dependent, not so much upon the food being fish, as upon the organisms which infect it. As may be gathered, the symptoms are such as have already been described, according as the infection is due to *B. botulinus*, *B. proteus*, etc. Diffuse scarlatiniform rashes so familiar after the consumption of mackerel, shrimps, oysters, are probably due to various bacteria and their toxins.

Special reference may be made, however, to poisoning by fish which has been contaminated with the secretion of various poisonous organs present in the same animal. Fugin, the poisonous body found in certain organs of the tetrodon of the Japanese and Chinese Seas, produces disturbance of the nervous and digestive systems, such as headache, restlessness, salivation, vomiting of large amounts of mucus or of blood, paralysis, cyanosis, dilatation of the pupils, and death from dyspnœa. So potent is this poison that it has been used as a means of committing

suicide. The gastric form of fish poisoning known to the Germans as Barbencholera is characterised by frequent loose evacuations.

The *Petromyzon fluviatilis* or lamprey, if not first treated liberally with salt, will cause, when eaten either raw or cooked, loose blood-stained evacuations.

Potato Poisoning.—From the uncertainty as to the agent really concerned in potato poisoning it is difficult to specify the symptoms that may be considered characteristic of the malady. Amongst the symptoms which have followed after the consumption of potatoes or food containing potatoes are rigors, fever, headache, giddiness, abdominal pain, cramps, drowsiness, diarrhœa, and vomiting; such a group of manifestations makes it very probable that the true cause is infection of the food by an organism capable of producing a toxic body, though it is conceivable that solanin may play a part as well.

The symptoms of mushroom poisoning have already been referred to, to some extent, in the description of the toxic substances separated from various poisonous mushrooms (*vide* p. 870). Kobert, adopting Husemann's grouping of the symptoms, describes different forms of mushroom poisoning or mycetismus. 1. Intestinal form.—Almost all mushrooms can, in certain circumstances, give rise to symptoms of gastro-enteritis, and some mushrooms, such as *Russula emetica*, are constantly liable to do so, but at present it is not known upon what substance this effect depends. In some cases the enteritis is so extreme as to resemble cholera—the "choleraic" form of poisoning. The intense diarrhœa in such cases is accompanied by severe abdominal pains, cramp in the legs, intense thirst, cold clammy sweats, suppression of urine, subnormal temperature, delirium, and coma. Usually the mild forms of gastro-enteritis come on almost immediately after the ingestion of the mushrooms, but the choleraic form may only supervene after the lapse of several hours. According to Dr. C. B. Plowright the *Ag. phalloides* is responsible for most of the cases of intestinal mycetismus; and was so for the four cases observed by him. The Helvella is also a frequent cause of this form of poisoning abroad. 2. The cerebral or nervous form is especially common after the ingestion of *Ag. muscarius* and its ally *Ag. pantherinus*, and depends in some cases not upon muscarine but upon the action of fungus-atropine and various toxalbumins. The common symptoms are dilatation of the pupil and an alternation of delirium and depression; muscular cramps have also been observed. As already observed the symptoms following the consumption of *Ag. muscarius* sometimes more closely resemble those of muscarine poisoning, as shewn by contraction of the pupils, salivation, slow pulse, and collapse. 3. Hæmatogenous Form.—Kobert includes, under this form, the effects which he originally described as due to the action of phallin, but admits that the evidence for this belief is based more on experimental than upon clinical evidence.

Diagnosis.—When symptoms arise in a number of people immediately after the consumption by them of certain foods which are recognised to be possible causes of food poisoning, such as fish, various

molluscs or tainted food, it is comparatively simple to connect the illness with the proper cause. Naturally, more difficulty will be met with when an interval elapses between the taking of food and the onset of symptoms. There may be still greater difficulty when the symptoms produced are referable to disturbances of the central nervous system, a possibility which is less thoroughly apprehended. It is obvious that when symptoms follow the ingestion of food which is generally considered quite harmless, and which when eaten is free from offensive odour, and to all appearance quite wholesome, the difficulties are exceedingly great.

Dr. Durham has pointed out that unexplained epidemics may depend upon contamination of food by the organisms of meat poisoning, and that in such cases the serum reaction may establish a correct diagnosis, even though the suspected food be no longer obtainable. Among meats, those rich in gelatinous material are especially prone to do harm. The addition of gravy-stock to food which in other cases has proved to be quite harmless may account for symptoms of food poisoning, for gravy-stock forms an admirable medium for the development of bacterial toxins.

Botulism and mussel poisoning attack the central nervous system, but the onset of the symptoms in the two cases is quite different. In mussel poisoning, according to Ostertag, symptoms may develop within less time than the limit given by Brieger, in less than even a quarter to half an hour after eating the food, and death may ensue within a few hours. The graver symptoms are not, as in the botulism, ushered in by long intervals of ocular disturbance.

Since cases of combined atropine and curari poisoning are extremely rare, it is unnecessary to do more than point out the similarity between botulism and this form of poisoning.

Meat poisoning may occur not only in extensive epidemics but may be confined to one or two individuals, and in this event the diagnosis is difficult. But as the outcome of Dr. Durham's researches this difficulty has been largely overcome, for, as already mentioned, the agglutination reaction of the blood of individuals suffering from meat poisoning makes it possible to obtain a certain diagnosis. By this means the varieties of meat poisoning can be discriminated. Dr. Durham's results have been confirmed by de Nobele (21).

It is hardly necessary in this article to discuss the numerous problems and difficulties involved in these agglutination tests, nor to enter into the refinements by which the groups of organisms known collectively as the *Bacillus enteritidis* group may be differentiated. It may be said, however, that these differentiations are rendered possible by the use of dilutions of various strengths and by the employment of experimental serums.

It is well known that human typhoid serum will cause agglutination not only of the typhoid organism but also of the *Bacillus enteritidis* and its allies; but the degree of dilution necessary for the agglutination

of the latter organism is much lower than for the *B. typhosus*. In the same way, an individual infected by any of the varieties of the *B. enteritidis* as the result of meat poisoning, will usually provide a serum which will agglutinate the *B. enteritidis* in higher dilutions than would be the case for the *B. typhosus*. Thus, Dr. Durham was able to shew that the particular variety of meat-poisoning organism, isolated from the liver of a patient in the Hatton epidemic, was agglutinated by the serum of 18 survivors in dilutions of 1 in 100 to 1 in 1000, whereas the typhoid bacillus was agglutinated by the serum of 5 of these 18 subjects with a dilution of 1 in 100; marked agglutination with *B. typhosus* was given by the serum of all the cases when the dilution was 1 in 20.

The task of diagnosing cases of meat poisoning would thus appear to be comparatively simple. For instance, the patient's serum would be tested against the typhoid bacillus, and a diagnosis of this infection would be excluded when the dilution necessary for agglutination was low; then the serum would be tested against various members of the *B. enteritidis* group, and if the degree of dilution at which agglutination occurred was very high, the diagnosis of infection by this organism might be confidently made. Unfortunately, there are certain difficulties in the way. In the first place the number of organisms which belong to the group of *B. enteritidis* is large. It is known, however, that these organisms fall into one or other of two groups possessing distinctive agglutination reactions, so that this difficulty is not a very great one. These two groups are separated the one from the other purely by their agglutination reactions, and the second group includes, besides the various strains separated by Dr. Durham, the bacillus of hog-cholera and other organisms, separated by van Ermengem, de Nobele, and others. Trautmann has grouped together a number of other organisms which are morphologically similar to *B. enteritidis* and which yet differ in agglutinating power. His five groups include, beside the meat-poisoning organisms, the two types of the paratyphoid bacillus, the *Bacillus morbificans bovis* of Basenau and others. The task of differentiating diseases depending on these similar organisms by means of different serum reactions may well cause dismay, but when it is remembered that all conform to one or other of a few common types of serum reaction, the task appears much simpler.

The second difficulty referred to above is that the serum of patients suffering from typhoid fever may react in as high (even higher) dilution on the *B. enteritidis* as upon the *B. typhosus*. The researches of Dr. Durham and de Nobele have shewn, however, that these difficulties are overcome by an appeal to the use of experimental serums. Thus, if an animal be highly immunised with the *B. typhosus*, its serum will react in much higher dilution (1 in 30,000) on the *B. typhosus* than upon the various members of the group of *B. enteritidis* (1 in 2000). The same means may be used to differentiate between the hog-cholera or Aertryke group of meat-poisoning organisms, and the other group of meat-poisoning organisms which possess an agglutinative reaction like that of the

bacillus discovered by Gärtner in the epidemic at Frankenhausen. It is also possible by this means to separate the *B. coli communis* from the meat-poisoning organisms.

Not only is the method elaborated by Dr. Durham of great value in distinguishing the various forms of meat-poisoning organisms the one from the other, and in differentiating them from infections by other organisms morphologically similar though widely different in their pathogenetic effects, but, as will be seen under the heading Prophylaxis, it can be employed to diagnose these infections in animals before they are slaughtered, and even to detect the infection in meat exposed for sale.

Dr. Sidney Martin (46) has studied the agglutinative power of the *B. proteus*, and finds that, like the toxins of *B. coli communis* and of *B. typhosus*, the proteus toxin leads to the development of an agglutinin fairly rapidly and in comparatively large quantities. Further study is required on the specificity of the agglutinating reaction of the proteus toxin before it is possible by this means to set at rest the vexed question whether the *Proteus vulgaris* is merely a harmless putrefactive organism or one which is seriously concerned in the subject of meat poisoning. Dr. Klein (35) has shewn that the serum of animals and of human beings affected with the *B. enteritidis sporogenes* does not develop any agglutinative property, which thus makes it impossible to diagnose such infection by serum tests.

The diagnosis of *mushroom poisoning* may be very difficult if the symptoms have followed upon the use of the liquid part of mushroom food; and when the symptoms occur several hours or even days after the eating of mushrooms, the association of the cause and effect may be overlooked. Fortunately, in many cases fragments of mushroom are discoverable in the vomit and dejecta; in suspected cases, examination should be made of the gastric and intestinal contents for remnants of the fungus.

The **Prognosis** in the various forms of food poisoning depends on the nature of the poisons present in the food. The mortality in epidemics of food poisoning due to the *B. enteritidis* group varies considerably between 1 in 5 to 1 in 200. In mussel poisoning the mortality is higher; 2 out of 30 persons affected dying in one epidemic and as many as 1 in 3 in another. Botulism has a high mortality, death occurring in 25 to 30 per cent of the cases. Intoxication by the products of the *B. proteus* is not as a rule followed by a fatal result. It is not desirable to quote the figures of the mortality following the ingestion of such ptomaines as mytilotoxine, tyrotoxicon, ptomatropine, etc., until these subjects have been revised in accordance with the great change which has taken place in the conception of food poisoning during recent years. In mushroom poisoning prognosis is difficult, as it depends not only upon the possible idiosyncrasy of the patient, but upon the amount of mushroom eaten, the completeness or incompleteness of its mastication, and the amount of toxic principles present in the food. The cases in which vomiting and diarrhœa follow quickly after eating the mushrooms are naturally more favourable than those in which the symptoms come on

some considerable time later. Yet other symptoms may develop, even when vomiting and diarrhœa have been well marked and prompt, and they may supervene several hours later.

Treatment.—PROPHYLAXIS.—Our national habit of cooking all meat much more thoroughly than in certain continental countries unfortunately does not obviate all risk of meat and fish poisoning. Since the endotoxins of the *B. enteritidis* are not destroyed even by boiling at 100° C. for thirty minutes, cooking sufficient to kill the organism still leaves their endotoxins intact in the meat derived from animals infected by this group of organisms. Infection of animals by these organisms may be suspected when they are suffering from enteritis, and, by means of the serum reaction, freedom from infection by the meat-poisoning organisms can be ascertained during the life of the animal. The agglutination test also provides a means of deciding whether meat which is exposed for sale is free from infection with the meat-poisoning organisms belonging to the group of *B. enteritidis*. One method adopted is to make a culture from the depths of the meat under examination; the cultivation tube is exposed from eight to twelve hours, to a temperature of 25° to 30° C. If bacterial growth occur in this interval the meat should be rejected. According to van Ermengem this test is reliable eight days after the slaughter of the animal, and even though the meat has already shewn signs of putrefaction. A more rapid preliminary test, introduced by de Nobele, depends upon the fact that the muscle-juice obtained from the flesh of animals infected with any member of the *Bacillus enteritidis* group is capable of agglutinating one or other of the two sub-groups of the meat-poisoning bacillus to which reference has already been made, low dilutions of 1 in 10 or 1 in 20 being used. The muscle-juice of healthy animals even in such low dilutions as 1 in 1 will fail to give any agglutination. The result may be worked out in about two hours; if negative, the slower method, described above, may be carried out as well.

The essential prophylactic measures against food poisoning by the simple putrefactive organisms are to prevent the occurrence of their growth by storage of food in suitable places, such as ice-chambers; and to condemn all food which does not appear wholesome, or has any odour of putrefaction. The *B. botulinus* causes but slight odour, or none at all, so that food infected by it does not arouse any suspicion. The symptoms of botulism are apt to occur in cases in which various forms of meat food are incompletely cooked; for instance, the outer parts of sausages may reach a high temperature during cooking, whereas the interior may escape. It is fortunate that a temperature of 80° C. is adequate as a means of destroying both the *B. botulinus* and its toxin, so that thorough cooking would thus prevent poisoning by these agents. Symptoms have only arisen when infected meat, ham, preserved meat, sausages, salted fish, have been eaten raw or incompletely cooked. Frequently such raw food becomes poisonous after being kept some weeks; in such circumstances if the meat be covered with gelatinous material, butter, or fat which serve as protectives, every opportunity is given for the development of

the anaerobic *B. botulinus.* Raw meat, even when eaten just after removal from a slaughtered animal, never causes the symptoms of botulism. Van Ermengem recommends that all meat having even merely a rancid smell should be excluded from use. Pickling of meat in a 10 per cent solution of salt will prevent the development of this organism. It is obvious that the greatest care must be taken in the storage of all articles of food which, as shewn above, are capable of providing suitable media for the growth of organisms. In all cases this requirement may be largely met by ordinary domestic cleanliness.

Shell-fish, such as mussels and oysters, which have been stored in waters contaminated by sewage, as shewn by the presence of the *B. coli*, should be unhesitatingly rejected. It will be remembered, however, that infected bivalves when placed in the open sea may be rendered quite innocuous. Shell-fish are so often eaten raw that excessive care is needed to ensure that they are wholesome. The knowledge that mytilotoxine is destroyed by boiling with potassium carbonate is of little use from the practical point of view. It is known that simply heating mytilotoxine to a temperature of 110° C. does not destroy its poisonous property.

In mushroom poisoning prophylactic measures are all-important. Many of the accidents in this country have occurred in children and young people who, out of ignorance, have eaten mushrooms which are usually avoided; for the same reason mushroom poisoning is more common in country districts than in towns, where inspection is more critical. It is a well-recognised rule that mushrooms should be cooked before being eaten, and consumed shortly after being gathered; and that remnants should not be served up again at a subsequent meal. Mushrooms should be well masticated, thereby securing more prompt digestion, and so obviating any prolonged stay in the alimentary canal and the possible subsequent formation of muscarine. Mushrooms which have putrefied would necessarily be rejected as articles of food, and mushrooms shewing parasitic invasion by other fungi should be discarded.

Immediate Treatment.—The readiest method of dealing with food poisoning is obviously to empty the alimentary tract. When symptoms arise soon after ingestion, and if vomiting have not already occurred, an emetic should be given at once, either of a simple form such as salt and water, mustard and water, or zinc sulphate, or an injection of apomorphine hydrochloride ($\frac{1}{20}$th to $\frac{1}{10}$th grain, or 5 to 10 minims of the injectio apomorphinæ hypodermica) guarded by a suitable dose of strychnine; it may also be advisable to wash out the stomach. When a longer interval has elapsed since the suspected food was taken, purgatives should be given in addition—for example, an ounce of castor oil or of the compound mixture of castor oil with 5 to 10 minims of the tincture of opium, or 3 to 5 grs. of calomel. Diuretic mixtures may help in eliminating the poison; in the event of very profuse and painful diarrhœa, purgatives should be withheld and sedative mixtures of bismuth and opium given instead, or small doses of calomel, or of hydrargyrum cum creta, may be given at frequent intervals

to assist in checking intestinal decomposition, without producing purgative effects. In cases of severe collapse diffusible stimulants such as ether or alcohol may be used, and coffee may be serviceable. Infusion of normal saline solution under the skin, or intravenously, would be of further help. The dietary should be of the simplest, and consist of milk, broths, and jellies. In cases of collapse and coldness of the extremities, brisk massage and the use of warm baths, hot bottles, and hot blankets may also be necessary. In extreme cases of choleraic diarrhœa a hypodermic injection of morphine should be at once administered. If the respiratory function threatens to cease as in poisoning by certain fish (tetrodon), artificial respiration may be necessary.

Pelzl describes three cases of botulism which ended in recovery. As the muscles of the œsophagus were paralysed, it was necessary to feed the patient artificially by means of an œsophageal tube. Irrigation of the bowel was also carried out, and pilocarpine in doses of $\frac{1}{6}$ to $\frac{1}{3}$ grain was administered by the mouth.

Mushroom Poisoning.—In the absence of any methods by which the toxic symptoms may be attacked directly, immediate treatment is mainly symptomatic and of the same character as that already described for other forms of food poisoning. The notion that muscarine is largely responsible for the symptoms has led to the indiscriminate use of atropine in all cases of mushroom poisoning; it should be restricted, however, to these cases in which the symptoms are really suggestive of muscarine poisoning, and as already shewn this is by no means universal; in other forms of mushroom poisoning atropine may be decidedly harmful, for example when delirium is present. In the choleraic form the use of morphine may be strongly indicated.

Causal Treatment.—As might be expected, the discoveries which have transferred so many examples of food poisoning from the domain of the chemist to that of the bacteriologist have led to the hope of a serum treatment for such cases. So far little has been accomplished in this direction, though there is some evidence that such treatment may be possible in the future.

Dr. Klein (35) was able to shew that the injection of guinea-pigs with non-lethal doses of *B. enteritidis sporogenes*, so far from leading to the development of immunity, caused them to be more susceptible to the organism. Fischer, working on the organisms of the meat-poisoning group, was unable to demonstrate in animals subjected to the injection of large amounts of cultures of these organisms any trace of development of antitoxic or of bactericidal properties, although the serum of such animals shewed a high degree of agglutinating power. Dr. Durham, however, found protective properties as well as agglutinating ones, in the serum of animals injected with the strains of the meat-poisoning organisms concerned in the Hatton and Chadderton outbreaks. Kempner has succeeded in obtaining an antitoxic serum against the *Bacillus botulinus* which is very active for animals. He shewed that this serum is capable of rendering animals immune to

subsequent inoculation or feeding with the *B. botulinus*, and that the serum is not only preventive, but curative, for by its means toxic symptoms experimentally produced were counteracted.

H. Batty Shaw.

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GRAIN POISONING

By Prof. T. Clifford Allbutt, M.D., F.R.S., and Prof. W. E. Dixon, M.D.

Rare and indeed virtually unknown as are the grain intoxications in our own country, we might well have been content with a brief reference to them. But the pathological interest of these cases is very great, both from a clinical point of view and from that of the experimental pathologist.

The damage done by the use of musty grain as food falls upon the nervous system, and, above all, upon the medulla and spinal cord; moreover, the influence of this part of the central nervous system upon nutrition is in no disease more remarkable. The effects of vasomotor disorder are also evident; and this is due to stimulation of some portion of the vasomotor mechanism situated probably between the spinal cord and the sympathetic nerve-terminations in the blood-vessels. The parallels between the effect of the grain poisonings and certain forms of spinal disease more common in this country are also very instructive. That Raynaud's disease, acrodynia, and erythromelalgia may be illustrated by the events of grain poisoning is indicated hereafter. There are three well-known modes of grain poisoning: Ergotism; Pellagra; Lathyrism.

Ergotism

Synonyms.—Epidemic Gangrene. Germ. *Kriebelkrankheit*

Although this work is not concerned with the historical aspects of medicine, yet a very brief account of the story of ergotism may not be out of place. Passing over the conjectural matter—such matter, for example, as the possible reference to ergotism in several places in the Old Testament; or, again, in Hippocrates and the Arabians—we come to a pestilence which was called "ignis sacer" by the chroniclers of the tenth to the twelfth centuries. This grievous disease at a later date was called "St. Anthony's Fire"; but under this name certainly more than one disease was included, especially erysipelas; which, indeed, was prob-

ably regarded, even by the physicians, as but one of the forms of the disease we now know to have been ergotism. Nomenclature was loose enough in the twelfth century. That St. Anthony's fire was often ergotism, at any rate, is almost proved by a woodcut reproduced by Dr. Ehlers, from Gersdorff, in which the saint is adored by a man who has lost his right foot; while his left hand, which he raises towards the saint, is represented, not as swollen, distorted, or ulcerated, but as burning with a living flame. Gersdorff entitles his chapter "Von dem heyssen Brand, den man nennet sanct Anthonius fewr." St. Martial was also more or less concerned with the pestilence. Syphilis and gangrenes, ulcers and witherings, were, of course, confounded with ergotism and with one another.

The ignis sacer of Celsus was an acute eczema; that of Virgil and Columella, probably malignant pustule (anthrax). Pliny, being a closer observer, describes several kinds of ignis sacer. Later writers took the name variously to signify malignant pustule, scarlatina, scurvy (Bateman), and so on. Ehlers says that to Thuillier belongs the honour of first detecting the part played by ergot in the tragedy.

The first epidemic which can with some certainty be ascribed to ergot is recorded in the annals of the convent of Xanten on the Rhine (1). The gangrene of ergot was not always dry; it is here stated that "detestabili eos putredine consumpsit, ita ut membra dissoluta ante mortem deciderent." A hundred years later the people of Paris were flocking into the churches to pray for cure of their sufferings from ergotism. In the same (tenth) century 40,000 persons are said to have died of the "feu sacré" in Aquitaine, Limousin, and neighbouring parts. "The cries of the sufferers were piteous; the stench of their limbs was intolerable; and many were carried off in a night." The only persons to come well out of the affair were the clergy, who received rich donations. The bishops of Aquitaine carried the relics of St. Martial in procession; when, indeed, as if by enchantment, the plague ceased. Ehlers maliciously suggests that the procession took place in the late spring, at which season the poison becomes attenuated. The scourge was most virulent in the end of the eleventh and early twelfth centuries, at the time of the Crusades. The harvests were bad and the bread discoloured. Dauphiné was so smitten that Pope Urban the Second founded a religious order at Vienne devoted to St. Anthony; an order to bring help to the afflicted. There were several hospitals of the order in France. That at Lyons, as Rabelais tells us, had its doors painted red, emblematical of the fire. Germany, Flanders, Burgundy, Denmark, and other countries suffered heavily, and even England. Whole districts were depopulated as if by the bubonic plague. The English epidemic is described as "an epidemic erysipelas whereof many died; the parts being black and shrivelled up."

Hugh of Lincoln is said by his chronicler to have seen many who had recovered from the fire, at Mont St. Antoine in Dauphiné. Horribly crippled, their health was nevertheless thoroughly restored; the cripples were of all ages, some lacked a forearm, others a leg, or even leg and

thigh up to the groin: all these stumps were soundly healed. To follow this woeful story through the thirteenth, fourteenth, and fifteenth centuries would be but to repeat the same piteous tale of poor and ignorant people, the sport of a malignant fate which a word of warning would have averted had there been any to utter it. The result was devastation, physical, moral, and civil. There is a grim humour in the story that the priests and sextons often suffered much, as the folk would pay the tithe in the lightest grain.

The evil was most destructive in bad harvests and times of famine; but after the middle of the thirteenth century we hear less of the sacred fire, although it lingered long in the current speech. Dr. Ehlers quotes an instance from Luther, "wie die trewen erzte thun, wenn das heilige feir in die bein komen ist." The plague, however, if less virulent was by no means stayed, as we shall see presently; and the medicine books still contained elaborate recipes for its cure. In the eighteenth century there was an epidemic in Denmark (Holstein) and also in Norway.

Slowly science did for these miserable peoples what the saints failed to do. The Abbé Tessier formed a good judgment of the conditions likely to promote an outbreak (he speaks of La Sologne): these are three—(i.) That the district was damp and foggy; (ii.) That the vegetable products were ill-thriven and stunted; (iii.) That the inhabitants were in bad health, being reduced by want and malaria.

Thuillier now discovered that the cause of the plague lay in the spurred rye; that the intensity of the malady is in proportion to the dose of this poison; and that the rye is spurred in damp and cold seasons. Experiments performed on animals corroborated and clinched the other evidence. Dodart, in the year 1676, was commissioned to investigate the nature of the disease; and in addition to previous observations he discovered that the ergot is most active when it is new, and loses much of its virulence as it grows stale. He describes the symptoms with some care and accuracy; to these, however, we shall return hereafter. C. N. Lange gave an admirable account of an epidemic of ergotism in the cantons of Berne, Lucerne, and Zürich, in 1709. He speaks of the excruciating pain which preceded and accompanied the gangrene; in many cases and epidemics pain was absent, but it was usually a terrible feature of the mediæval ergotic plague. Lange also traces the pest to ergot in a very careful way. This epidemic spread in Dauphiné and Languedoc; and we have a full account of it in the archives of the Abbaye St. Antoine at Vienne. The ruthless persistence of the malady is again noted, the victims often being in torture for six months or more before the release of death. The physician of the abbey also notes the devouring fire which burns the affected parts, cold as they appear, with intolerable pains. He describes the gangrene as of the black and dry variety; but another doctor of the abbey saw many cases in which the gangrene was not altogether dry, but suppurating, stank horribly, and was filled with worms. Four hundred parishes in this part of France were attacked—men, women, and children indiscriminately.

In 1746-47 there was a terrible outbreak in Sweden, Russia, Sologne again, les Landes, Artois, Flanders, and other places. In this epidemic pain was most violent; so that the fire in the limbs drove the victims hither and thither—some in their agony hurling themselves against the walls or even into the water. Those grievously attacked generally died; those who survived became blind, dumb, or demented. Salerne experimented with the poison on pigs, ducks, and fowls; and the animals died of gangrene. He corroborated the statement that the fresh ergot was the most virulent, and that after some months it sweated and lost its poisonous properties. About this time Linnæus led observers into error by alleging that the malady was due to the radish (raphanus); and thus his authority led to the name of raphania for ergotism. It does not appear that Linnæus had ever visited the ravaged districts; and it has since been shewn that the raphanus is never poisonous. Later in the eighteenth century there were many severe outbreaks in many parts of Europe; one of them (small in extent) in Suffolk. An observer in one afflicted district found an average of twenty spurred grains in each handful. Wagner reported one-fifth of a bulk of rye to be spurred; and Bryce says that 10 per cent of the meal might consist of ergot.

Ergotism has by no means ceased in Europe: it is, however, almost confined to the Russian Empire, in many parts of which it seems to be still endemic. Speaking generally, a better knowledge of the causes of the disease and of its treatment has lightened the weight of the plague. Still many and grave cases are seen; and during the last century many epidemics in many parts of Europe have been described. The year 1845 seems to have been very fertile in ergotism: in 1881 there was a great outbreak in Ekaterinoslav; and in 1883 a like outbreak occurred in Tomsk—out of 300 patients 36 died.

The convulsant form of ergotism, which does not produce such highly characteristic effects as the gangrenous, has not received the same historical recognition as the latter. Our first account dates from the sixteenth century; and it is particularly noteworthy that the descriptions of epidemics of convulsant ergotism come from countries which have been less frequently the seat of the gangrenous form, and not from France, where the latter form of the disease has been most prevalent from the earliest to modern times. The gangrenous and the convulsant forms have always had almost entirely distinct areas of distribution, each disease appearing time after time in its own territory as a widespread epidemic. In only a few epidemics have both forms been observed together.

To avoid detaining the reader by a description of the most recent and therefore most scientifically described epidemics, we content ourselves by giving, in the list of references, the titles of the most important of the reports and studies of recent years.

Causation.—Ergotism is due to one or more poisons which, under certain conditions, are elaborated by the fungus Claviceps purpurea; remoter causes are starvation, misery, and ill-health. Epidemics thrive

only under conditions which are favourable to the growth of this parasite; that is, after a damp season, and particularly in years when a hot and dry summer has followed a very rainy spring, especially when the grain has been grown in marshy districts and in the shade. Ergot affords one of the most noteworthy examples of a plant which elaborates different substances according to the climatic and other conditions under which it is grown. Papaver somniferum grown in Turkey yields an opium very rich in morphine, but in the British Isles the same plant produces an opium containing a mere trace of the alkaloid. And so it is with ergot; unless the ergot is grown under certain conditions, and these have not yet been precisely laid down, it elaborates little or none of the active principles to which its medicinal virtues and poisonous properties are due. The cause of the inactivity of so much of the modern ergot is no doubt to be found in the improved conditions under which rye and other cereals are now grown. Grain is now brought into Europe from America, India, and other parts, competition is more acute, and so the plants are sown in Europe only upon suitable ground, which in most cases is properly prepared and drained. These conditions are not very favourable for a free growth of ergot, and the fungus is apt to lose its power of producing the poisonous constituents of the plant. These considerations indicate the reason for the decline of epidemic ergotism; rye, which is the commonest cereal attacked by ergot, is eaten by man less than formerly; ergot is less prevalent, and what there is tends to be less active.

That our knowledge of the composition of ergot is in a very unsatisfactory condition is principally due to the instability of its active principles. The active bodies so far separated do not crystallise, and have no characteristic chemical reactions; it is probable that they have not been isolated in a pure condition. The most reliable work has been done by Kobert and Jacoby; as a result of their researches three groups of bodies have been isolated. First, ergotinic acid, a nitrogenous glucoside with the properties of the sapotoxins, is a gastro-intestinal irritant, but is not absorbed when taken by the mouth, so that beyond causing some vomiting and diarrhœa it is not likely to lead to evil effects. A second substance, cornutine, which is probably a mixture of several alkaloids, has an action resembling that of picrotoxin, and produces its effects by excitation of the central nervous system, more especially the medulla. In poisonous doses cornutine produces clonic convulsions. The third has been termed by Kobert sphacelinic acid; according to Jacoby it is a mixture: he has isolated a nitrogen-free resin sphacelotoxin which he regards as the active principle or the gangrene-producing substance. This body does not exist free in the crude ergot, but is combined with ergochrysin as chrysotoxin, or with an alkaloid secaline as secalintoxin. Sphacelotoxin increases the tonus and peristaltic movements of most of the plain muscle throughout the body, especially of the vessels, which become so intensely constricted that stasis may occur in certain of the peripheral parts of the circulation. The vaso-constriction is associated with the

pouring out of a hyaline substance that more or less completely blocks the smaller vessels, and results in peripheral gangrene; the walls of the larger arteries become thickened, and their lumen is diminished. The action of sphacelotoxin is certainly not peripheral, for we have frequently shewn that perfusion of the drug through isolated vessels never leads to diminution of their calibre; according to Dr. Dale it corresponds with an excitation of the cranial and sacral autonomic, and also of the true sympathetic nerve-supply to all organs containing plain muscle.

There is, therefore, reason to believe that the two varieties of ergotism, the gangrenous and the convulsant, are caused by the varying amount of the two constituents cornutine and sphacelotoxin present in the ergot.

In the case of ergot, as of some other poisons, certain persons are said to be peculiarly susceptible to its effects, and medicinal doses of ergot have been followed by severe poisoning. An explanation of this is no doubt to be found in the extreme variability of strength of the extracts of ergot. We have pointed out elsewhere that by far the greater number of these at present on the market are quite valueless, in that they possess little or no power of constricting vessels or exciting the uterus to contract. Occasionally, however, a very active sample may be met with, and it is suggested that the rare cases of poisoning which have been described after the administration of medicinal quantities of ergot are caused by the use of such a sample. There is, however, evidence that some persons are more susceptible to ergot than others, because not infrequently during epidemics of ergotism some members of a stricken family escape; other patients are sporadically victims in the midst of general immunity. Again, those persons must suffer first and chiefly who are mainly or altogether dependent on the diseased corn for food. Thus cattle died first in some epidemics; and those labourers whose food was but bread and water. So long as milk, cheese, or meat formed part of the diet the peasant suffered less severely or not at all. The proprietor who dressed his own corn was better protected than the workmen who had to take their corn from the miller, who bought the cheapest grain he could get.

Pathology.—The sensory nerves are paralysed, but it is uncertain whether the action be central or peripheral (Brunton). The muscles and motor nerves are unaffected. Dr. Mitchell Bruce says that the posterior columns of the cord shew sclerosis somewhat resembling that of tabes dorsalis. The arteries are thrown into a state of contraction, producing a rise of blood-pressure. In some measure, however, this rise is due to stimulation of the vasomotor centre in the bulb, although the main action is on sympathetic nerve-cells; none of the action is peripheral on the vessels. In the constricted and thrombosed arterioles a glutinous matter (decolorised plasma ?) is found, and the walls of the vessels, either primarily or secondarily, undergo a hyaline degeneration, especially of the tunica intima. The blood drawn during life is dark and viscous. After death the abdominal viscera are found "inflamed" (Brunton); and the lungs

are always in a state of congestion. Ehlers repeats the serious warning, therefore, against the use of ergot in enteric fever, in which disease it may do fatal mischief. The uterus, intestines, and bladder are tetanically contracted, and the continuous medicinal use of ergot is apt to do grave harm.

The detection of ergot in flour is thus performed:—a small quantity of the sample is mixed with ether, and a few crystals of oxalic acid are added; if the liquid, after being boiled and allowed to become clear, exhibit a red tinge, ergot is present in the sample (Böttger).

Symptoms.—Ergot may prove fatal by acute intoxication or by slow torture. It may occur in two chief forms at least, the spasmodic or convulsive, and the gangrenous—the variation being probably due to the variable quantities of two or more poisonous principles in the spur. In the acute form, which is more common in children, heaviness of the head, giddiness, depression of spirits, and formications may pass rapidly into colic, tympanites, clonic and tonic cramps (Krummekrankheit), precordial anguish, violent vomitings, purging, and stupor, with or without convulsions (epilepsia epidemica): if death ensue in one or two days, as is not infrequent, the seizure is not unlike cholera, but with a more clouded sensorium. A vesicular eruption has been seen in some cases. If convalescence follow an acute attack, which is a rare result, it is very tedious and imperfect, broken by relapses, and dogged in after-time by such sequels as epilepsy, weak-mindedness, cataract (Taube, Meier, Graefe), and many other misfortunes. The gangrenous form may also set in with terrible vehemence, though of course for the destruction of the limbs more time is required. The agonising pain may penetrate the affected limb, or limbs, like a fire; but, on the other hand, there may be no pain. An erysipelatous blush may precede lividity; but usually it is absent, and the lividity passes into darkness or blackness. As a rule the gangrene is dry; but moist gangrene is seen occasionally. An inflammatory band marks off the dead part, which separates without hæmorrhage. More than one limb may be affected; and part after part, until the body and viscera are involved, and death ends the ruthless course of the disease. At first the blood-pressure is raised: the radial artery is felt to tighten from day to day, and the pulse becomes very small; as the disease advances it becomes almost or quite imperceptible. When the mischief is arrested at an earlier stage, and the poor sufferer recovers, he is probably crippled by the loss of hand, foot, or limb.

The malady may pursue a very chronic but not less pitiless form, when all the symptoms invade the body very gradually. The erysipelatous skin may die first and become detached like the slough of a snake. Again, there may be a mixture of the spasmodic and gangrenous symptoms in the same patient.

In mitigated attacks there may be little more than heaviness of the head, melancholy, some creepings, and slight tonic contractions of the legs; the appetite may not fail, and the paresis may not go beyond anæsthesia. In this stage it is not uncommon for patients to be so

anæsthetic as, for example, to sew a finger to needlework. It is a good sign when the creeping returns; an irritation may follow, annoying enough, but welcome, as in recovery from frost-bite; heat returns to the cold limb, and the characteristic pallor of the face gives place to a freshening tint. These recoveries are more common in the spring and early summer before the new grain comes into use, and as the old spurs are losing their virulence.

Diagnosis.—Ergotism, only too easily recognised in times of epidemics, may not readily be detected in sporadic and mitigated cases. Ehlers does not hesitate to raise the whole question of the relation of other diseases marked by ischæmia of the extremities to ergotism; such as acrodynia, Raynaud's disease, and erythromelalgia. As to acrodynia, Ehlers unhesitatingly attributes the cases described by Rayer to ergot. The disease arose spontaneously, appeared epidemically, and in damp seasons. The symptoms certainly presented the characters of ergotism. Ehlers alleges that ergotism and Raynaud's disease arise at the same season; that Raynaud was mistaken in supposing that ergotism respects certain ages or one sex; and, finally, that the cases Nos. 9, 12, and 15 of Raynaud were certainly ergotism. No. 9 and No. 12 were in patients who ate rye habitually. In the young woman, No. 15, a gramme and a half of ergot had been administered in her confinement three days before the symptoms began. Robert relates a case in which sixty centigrammes of ergot caused gangrene in a woman shortly after confinement, and death a month later. In other cases Ehlers hints that young women may forget to inform their medical adviser that they have been taking ergot, even if they were aware of the contents of some medicine taken for abortion. Other cases, he thinks, were too indefinite in character to permit of an accurate diagnosis. We must add, however, from personal knowledge as well as from the evidence of his treatise, that Raynaud did not overlook the possibility of ergotism in his cases, and decided against this poison.

In 1872, and again in 1878, Dr. Weir Mitchell described a group of symptoms under the name of erythromelalgia, and reported six cases. Many cases have subsequently been put on record [*vide* Vol. VI.]. One of these, recorded by Nieden, is pronounced by Ehlers without hesitation to be one of ergotism: he is disposed to put the same interpretation on others of these, and urges that all these cases should in future be studied in the light of ergotism. The differences, however, are notable enough. The superficial resemblance of acute ergotism to cholera has already been mentioned; confusion between the two maladies is not likely to arise.

Prognosis.—The mortality in severe epidemics may be as high as 60 per cent; in the less severe it may fall as low as 10 per cent. As is pointed out in another section, the symptoms of gangrene may pass off and the limb recover; but this event is not to be anticipated. Acute ergotism is generally fatal. In chronic cases much depends on the dose of the poison and on the subsequent prevention.

The **treatment** of ergotism must be largely symptomatic. Acute

cases, in which death may result from collapse, should be treated like other forms of irritant poisoning: the stomach must be emptied either by the tube or emetics, stimulants administered, and external warmth applied. After the poison has been absorbed into the system the circulatory and nervous symptoms must be treated as they arise, in much the same way as in cases of chronic poisoning.

In chronic poisoning of whichever form an endeavour should be made to trace the source of infection; not always an easy task in sporadic cases; the pernicious grain or drug must be at once withdrawn and the patient placed on light food of approved source. The patient must be kept warm, and in the more severe cases put to bed. Drug treatment is necessarily palliative; in the gangrenous form we have to fight against the stimulant action of the drug on the sympathetic nerve-ganglia; it is this action which produces the intense vaso-constriction and the very large increase in systemic blood-pressure. To counteract this effect drugs should be given which exert a depressant action on these same nerve-ganglia; such drugs are conium, lobelia, and the alkaloid sparteine. Sparteine is the best drug for the purpose, because it is much less poisonous than the others; it should be pushed until the blood-pressure is appreciably lowered. In very severe cases, however, it may be necessary to supplement the sparteine with drugs which directly paralyse the vessels, such as the nitrites. Motor nervous affections, such as twitchings, tremors, spasms, and convulsions, as we have already pointed out, are caused by excitation of the medulla, and should be treated by drugs such, for example, as chloral, which depress this structure; when convulsions are severe the patient may be kept under chloroform for a time. Small doses of morphine may be used to relieve the sensory effects. The bowels should be made to act freely, saline aperients being most useful for this purpose.

Pellagra

This disease, which presents many analogies to ergotism, is due to a poison the nature of which, like the poison of ergot, exerts its effects mainly upon the central nervous system.

Pellagra is at times epidemic in its invasion; at other times or places it is endemic or sporadic. It appeared for the first time in Europe some fifty or sixty years after the introduction of maize from America: it broke out first in Spain and spread later to France, Lombardy, and elsewhere. Casal, in 1750, described the disease in the Asturias under the name of *mal de la rosa*: the Asturias are still its headquarters in Spain. Frapolli of Milan termed the disease pellagra in 1771. In Italy, Dr. Creighton tells us that it first broke out in the neighbourhood of Lago Maggiore; and in 1750 it rapidly extended its ravages in North Italy. Its extension in the Emilia and in Tuscany has taken place during the last century. In Central Italy it is little known; in South Italy and Sicily it is not seen at all. In 1881 there were 103,958 pellagrons in Italy; and in the year 1903 the death-roll from this disease was stated

to be 2648. Antonini has shewn that pellagra has been receding in some provinces and increasing in others. The number of pellagrous patients varied from 0·12 per 1000 of the agricultural population in the least affected areas to 50 per 1000 in others, such as Perugia, Cremona, and Padua. Like ergotism, pellagra is a disease of the poor, especially of the poorest. The Italian peasantry are for the most part in a wretched condition; they are ill-clad, ill-fed, oppressed by hard labour, and housed in huts scarcely fit for the domestic animals. The pestilence was formerly very prevalent in Rumania; in 1888, 10,626 persons in Rumania, out of a total population of 5,339,650, were suffering from pellagra. Since 1856 the disease has shewn itself in Corfu. In still more recent times, pellagra has spread to Egypt, and in certain provinces apparently has affected a very large proportion of the poorest peasants. Dr. Sandwith examined 315 men, presumably healthy, in eleven different villages in the province of Gharbieh, and of these 36 per cent shewed signs of early pellagra. Yet they stoutly denied that anything was wrong with them. Pellagra is practically unknown in this country; a supposed case has recently been published (41A); but, as neither the symptoms nor the physical signs were characteristic, the diagnosis must remain doubtful.

Causation.—Although pellagra, like ergotism, is associated with bad food and water, misery, and grinding labour, yet these conditions, which favour the disease, are not sufficient of themselves to produce it: the peasantry in Southern Italy are even more miserable than those of Lombardy. A more specific cause is necessary; and there is now no doubt that this immediate cause has been traced to bad maize. There are three circumstances in the history of pellagra which throw some light on its origin:—first, that pellagra has appeared only in comparatively recent times, after the introduction of maize from America; secondly, its distribution is very restricted, and that endemic foci exist only among rural populations; and thirdly, that epidemics invariably follow the abundant use of maize; where it is not cultivated or consumed pellagra is absent. Dr. Creighton points out that although maize forms a large part of the staple diet of the peasantry in countries other than those subject to this plague, yet beyond its ordinary haunts pellagra does not occur. "Compared with the maize zone the area of pellagra is a mere spot on the map." Even in countries such as Burgundy, Franche Comté, and the Bresse, where the climate and soil are somewhat trying for maize, pellagra rarely appears; in these provinces the greatest care is taken to dry the grain before it is stored, yet after a particularly bad harvest pellagra may arise. These considerations make it very improbable that, as De Giaxa insists, sound maize may set up the disease in susceptible persons.

Pellagra is less prevalent where the maize is supplemented by other foods. Corfu, as Dr. Creighton points out, is almost a crucial instance: maize thrives well there, but its culture has been largely displaced by vine culture; since this change maize has been imported, and the

importations consist of the inferior maize of Rumania still more deteriorated during a long water transit by the Danube and Black Sea. The Wallach peasantry of Rumania, who are subject to pellagra, gather the corn before it is ripe, and shoot it into pits, where it becomes musty. In lower Egypt the poorest and most careless of the peasants sow diseased maize seed, gather the crop before it is ripe, store it in damp places before it is dry, and leave the cobs within their sheaths. The peasants in upper Egypt are equally poor and ignorant, but they are saved from pellagra because their stable diet is not maize but millet. In Northern Italy the peasantry grow the more worthless kinds of maize on poorly cultivated grounds, sow it late, harvest it before its maturity, and carelessly store it undried. The millers grind the cheapest corn for the peasants' use ; moreover, the loaves are unleavened, half-baked, and turn mouldy before they are consumed. This kind of evidence goes no farther than to indicate that the poison is due to ordinary putrefactive changes—changes due, no doubt, to microbes, but the microbes concerned may be the ordinary agents of decomposition : the special characters of maize poisoning may be due to some peculiarity in the chemical structure of this grain itself. One fungus to which the disease has been attributed is the *Reticularia ustilago*; its spores are seen as a brown or greenish-brown powder which is deposited under the epidermis. This fungus is found in other diseased grain, yet in the case of maize only is its invasion followed by the pellagra. Whatever be the nature of the organism there can be no doubt that the symptoms of pellagra are caused by some poison produced in diseased maize. Balardini performed some experiments with pellagra-maize upon men and animals. Fowls which were fed on such maize became thin, lost their feathers, and later their power of movement. Men were affected principally with digestive troubles and diarrhœa. Lombroso made some more exact investigations. In fowls he observed diarrhœa, casting of the feathers, and death ; in rats, wasting, choreiform movements, and death ; in healthy men after a prolonged course of a tincture prepared from the maize, loss of appetite, vomiting, diarrhœa, desquamation of the skin, malnutrition, and dilatation of the pupil. He prepared from the pellagrous maize a fatty oil and an extractive substance, pellagrozein, which are never found in sound maize, but which can be artificially produced in the corn when it is exposed to fermentation. Cortez, working in Husemann's laboratory, has experimented with the toxic substances obtained from maize by Lombroso, and confirms him in almost every point. Procopiu even states that alcohol distilled from damaged maize may give rise to pellagra. Nevertheless Ceni, following up his work with Besta, has recently stated that he has found aspergillus in 21 out of 28 cases of pellagra. And in one woman who died of pellagra-typhoid the mesenteric glands, which were enlarged and copper-red in colour, yielded *Aspergillus fumigatus* on cultivation ; it is not stated whether the spores were seen in sections of the glands. Ceni offers no adequate reason why cultures taken from those dying of acute pellagra give negative results, and his experiments are quite

insufficient to modify our present views on the nature of pellagra, that it is a poison formed outside the body.

Pellagra is chiefly a disease of middle life, and of women more often than men; but children are attacked not infrequently, and Dr. Creighton, treating of its heredity, says that infants at the breast may shew signs of it; he adds, however, that such infants are partly fed on the household polenta.

Pathology.—Whatever the poison, its effects, as in the case of ergotism and lathyrism, fall directly upon the nervous system, and the main external features, such as erythema and gangrene, are secondary to changes of the nervous structures, whether of vasomotor or directly "trophic" origin. Although the vasomotor changes are not so definite as in ergotism, yet in pellagra they seem to be of no small account. The most obvious changes are found, however, in the spinal cord; and these are precisely such as the palsies would lead us to expect. Both in ergotism and in pellagra the posterior columns are injured. In the most painful cases of ergotism the posterior root-zones are attacked; in pellagra, as the report of the clinical symptoms would indicate, the lateral columns rather are implicated. The weight of the disease falls on the crossed pyramidal tracts. The direct cerebellar tracts are never touched. The cells in the anterior horn are deeply pigmented; but the muscular atrophy of the later phases of the malady is general, not particular. The lesions of the posterior columns fall chiefly upon the cervical and upper dorsal region: those of the lateral column rather upon the middle and lower thirds of the dorsal region. Pigmentation also is found in other internal organs and in the skin. Dr. Sandwith (50) has studied the spinal cord in three cases of pellagra poisoning. In the first case there was some degeneration of the posterior columns as shewn by Pal's method of staining; a degenerated root entered at the third lumbar, and could be traced up to the dorsal region; the posterior medium columns were unduly pale. In the second case well-marked degeneration of the posterior columns was present, evidently of root origin: there was also an increase of connective tissue in the area of the affected roots, and some thickening of the walls of the arteries. The posterior roots also shewed marked degeneration in their extra-medullary course. The third case shewed only some doubtful alterations in the medullary sheath of certain nerves. He suggested that the sclerosis of the posterior columns was of root origin and that the increase of connective tissue in these columns was secondary to degeneration of the roots. In pathological character the changes seem rather to be extremely slow degenerations than inflammations: they are probably not essentially of a progressive kind; the advance of the mischief, at any rate in the earlier stages of the disease, depends on the persistence of the causes. The brain presents general wasting; the ventricles are somewhat distended and contain some excess of fluid. The stomach may be dilated.

Symptoms.—Pellagra has three characteristic groups of symptoms which are associated with (1) the skin, (2) the alimentary canal, and (3) the central nervous system. In the spring-time the patient complains of

bodily weakness, headache, depression of spirits, sleeplessness, cramps, vague but often severe pains in the spine and joints, vertigo, and dyspepsia. As the malady progresses the skin disease appears, though the eruption is not constant; there may be "pellagra sine pellagra."

The eruption is an erythema which chiefly affects the parts exposed to the sun; the backs of the hands and feet become shiny, tense, and red. The skin is swollen and is the seat of burning or itching sensations; petechiæ are frequent, and bullæ appear, which on rupturing leave indolent ulcers (pellis agria = ulcer of the skin). In about a fortnight from the beginning of the attack the erythema subsides, and desquamation follows, leaving the underlying skin thickened and stained of a light sepia colour. The symptoms usually subside in the autumn, to reappear in an exaggerated form in the following spring. The attacks thus recur regularly every year, the thickening and pigmentation being increased on each occasion in the first four or five years. Afterwards the integument undergoes atrophy, and becomes dry and wizened as in old age: this atrophy is especially marked on the backs of the hands. The nails and hair shew no change.

In the later stages diarrhœa sets in. The dyspepsia seems to be the first disorder to follow the invasion of the poison (T. C. A.). In severe cases free hydrochloric acid may be altogether absent; in all it is much reduced. A deficiency of hydrochloric acid in the gastric juice is not, however, in any way characteristic of pellagra, as has been asserted: such a deficiency is present in most forms of wasting disease. Digestion is therefore slow and imperfect; peptones are deficient, and the catarrhal discharge facilitates the lactic and other fermentations. Agostini states that careful attention to this stomach derangement, including lavage, is of benefit in pellagra.

When the patient has thus been the subject of the disease in its recurring attacks for three or four years his depression of spirits deepens into melancholia of a severe and irremediable kind. He commonly suffers from globus. The melancholia may be altogether dull and heavy, or on the other hand it may have maniacal phases: the patient may be moody, self-accusing, and remorseful, or he may present maniacal periods, in which misery or a horrible burning of the skin may drive him to suicide. Systematic monomania ("paranoia") is never seen. As depression may alternate with mania, so stupor may alternate with the vertigo: and twitchings, tremors, and even epileptiform seizures of the cortical variety are not uncommon. The cramps, likewise, may pass on into permanent contractures.

Palsies form part of the ordinary course of the disease: the knee-jerk may differ on the two sides, but in the large majority of cases it is increased; it is rarely absent. Tendon reflexes are often to be detected in the forearms. The gait, though uncertain, is never ataxic; it rather assumes the form of spastic paraplegia. Ankle clonus, though often present, is not invariable. These paretic symptoms are commonly preceded by tremor. Sensation is virtually unaffected.

Together with this degeneration on the side of the nervous system the whole man also deteriorates. Flesh and strength fall away, the mental faculties wane, and life is but too often prolonged to the dregs, to be cut short at last by colliquative diarrhœa. With each successive year, to use Dr. Creighton's words, the patient becomes more like a mummy: his skin is shrivelled and sallow, or even black at certain points; his bones protrude; his muscles waste; his movements are slow and languid, and his sensibilities grow more and more obtuse. The disease is sometimes so chronic as not to shorten life, and it is rarely very acute.

Diagnosis.—In countries where pellagra is known there can be little difficulty in detection of the malady, even in its earlier stages. The only diseases to which it shows any likeness belong to the same class of progressive dementias. General paralysis of the insane might at certain moments present some resemblance to pellagra; but the character of the lesions of the limbs or, if in rare cases these be absent, the lack of grandiose ideas, the features of the palsy, and the history of the origin of the attack, would direct the observer to a true opinion. The speech may be affected in pellagra, but not in a characteristic fashion. The pupils are never fixed as in tabes, but some myosis is often present. Cases are, however, recorded of the coincidence of the two maladies in the same person. The disturbances of sensibility, if any be present, and the eruption may suggest leprosy; and leprosy, like pellagra, may present remissions if not definite seasonal phases. In nodular leprosy, however, the granuloma of the skin, and in anæsthetic leprosy the nerve-changes, are characteristic. The colour of the skin may not be unlike that in Addison's disease; but the eruption, or in its absence the nervous symptoms of pellagra, would suffice to indicate this disease.

Prognosis.—When the disease has recurred for three or four seasons, and especially if the mind be affected, the prognosis is very bad. One of us [T. C. A.] gathered from the physicians of the Italian lunatic asylums that recovery of patients once arrived at the asylum stage of insanity is almost unknown. Still, these are extreme cases; the mentally afflicted in their earlier phases may recover: too often, however, the advance of death is inexorable.

The only **treatment** is to remove the causes of the intoxication, and of the failure of resistance; and thereafter to treat the symptoms on general principles.

The Ministry of Agriculture in Italy has provided drying apparatus for grain, bakeries, and other hygienic advantages, including better house accommodation, in the infected districts; also "pellagrosari," or places for the treatment of "pellagrosi," for those patients on whom the disease has gained a hold. It is stated (41) that a decrease of the malady has followed on these reforms; except in the district of Perugia, in which, for certain incidental reasons, the malady seems to have increased. Dr. Sandwith has suggested that in Egypt the peasants and employers of labour should be taught the early symptoms of the disease. At this stage it will yield to treatment, but if neglected the symptoms increase in

severity and end in insanity or general debility, which entirely unfits the individual for work.

Lathyrism

This is the name given by Cantani to another *mal de misère* due directly to diseased grain, and more remotely to wretched conditions of life. At the end of the eighteenth century, and at the beginning of the last, suspicions arose that certain palsies of the legs were due to the use, as food, of the *Lathyrus sativus* and the *L. cicera* (or chick-pea). *Lathyrus sativus* is indigenous from the southern Caucasus to northern India; it is now cultivated all over India. Nevertheless, poisoning by the various species of the family Papilionaceæ has been known from very early times, for it is stated in the Hippocratic writings that "at Ainos those men and women who continually fed on pulse were attacked by a weakness in the legs which remained permanent": and again, in Don's system of gardening it is stated that bread made from the flour of pulse led to an epidemic in the seventeenth century, and that subsequently an edict forbidding its use was promulgated. The disease has been observed in the departments of Loire et Cher, in the Abruzzi, at Alatri, at Allahabad, and in Kabylia. No poisonous substance has been separated from the pulse. Some authorities, including Sir P. Manson, have suggested that the disease may be due to a poison produced by microbes growing on the pulse (compare pellagra and ergotism); but this speculation is not supported by any evidence. Two features of the disease, as it occurs in India, are its seasonal incidence—lathyrism always breaks out in the rainy season—and its marked preference for males, only about one female being affected for every ten males. These data have led Major Hendley to believe that lathyrus disposes to the disease, but that severe cold and damp are required to excite the sudden seizure. An exclusive or almost exclusive diet on the chick-pea, and wretched conditions of life, seem, as in the two preceding diseases, to be accessory causes. The outbreak at Allahabad, described by Dr. Irving, followed a failure of the wheat crop. Major Hendley describes an outbreak in a village in which 10 per cent of the male population had quite suddenly become more or less severely paralysed in the lower limbs. All those affected—poor hand-to-mouth labourers—had subsisted for some eighteen months on the pulse of *Lathyrus sativus*.

Pathology.—Lathyrism is a milder disease than either of the preceding kinds of grain poisoning; hence no doubt the great imperfection of the post-mortem records. Such notes as "softening of the cord," and other such inaccurate and vague phrases, give us little information; at present, therefore, the precise lesions can be inferred from the symptoms only. These, we need scarcely say, point to the lateral and posterior columns in the lumbar region as especially the seat of the activity of the morbific agent, whatever this may be.

Symptoms.—Lathyrism is a quicker disease than either of the two

preceding, and not so ruthless. A patient may go to bed, apparently quite well, after a hard day's work in the rain and awake in the morning to find himself unable to get out of bed; his limbs are stiff and creepy, and in some epidemics much pain in the back is complained of. During the next few days weakness increases, progression becomes difficult, and tremor and uncertainty are observed in the hands. Both legs become weak at the same time, the calves being first affected and then the thighs; the peculiar gait is due to the great weakness and to the increased reflexes. The accounts of the disease often describe a peculiar rigidity of the dorso-lumbar muscles set up on the side opposite to each leg as it is advanced in turn; giving a throw of the trunk backwards and sideways against the weight of the advancing leg. Thus, as the patient walks, the head and body must be thrown into a succession of curves, describing a screw or a chain of figures of eight. The leg, on the other hand, with the toe pointed and the heel drawn up, is thrust out with a tremulous extension and adduction; thus the toe reaches the ground before the heel, or the heel may never reach the ground at all, and the gait become a tripping on the toes. In some epidemics the gait is said to have more of an ataxic character, and the pain to be greater; as if the poison fell more on the posterior columns.

The disturbances of sensation seem to be no less remarkable. Hyperæsthesia and paræsthesia of the legs may be followed by anæsthesia, when the skin reflexes are lost; but in other epidemics sensation is not affected. The tendon reflexes, however, are intensified. Intolerable creepings, as in ergotism, also torment the sufferer. The application of the hot moist sponge to the spine calls forth this creeping and tremors of the legs.

The evolution of these various symptoms takes four or five weeks. The sphincters are not affected as a rule; but in severe epidemics and in bad cases both anal and vesical sphincters are said to be palsied. Retention of urine is more common. Sexual power is enfeebled or lost. In none of the accounts is mention made of the arms, save as being occasionally tremulous. Cutaneous affections such as urticaria and bronzing are occasionally observed. The mind, speech, and pupils invariably escape and the patient has no sense of illness.

Diagnosis. — The only disease which simulates lathyrism at all closely, is Erb's syphilitic spinal palsy. The epidemic occurrence of lathyrism, and probably the absence of all syphilitic antecedents, will suffice for distinction. In case of doubt the grain may be tested on animals.

Prognosis seems to be more favourable than in the two former kinds of grain poisoning. If the diet be changed before the cord has become deeply disorganised, recovery may be anticipated.

Treatment at present consists only in this change of diet and in reform of other adverse conditions of life.

Domestic animals are liable to lathyrism. Some authors assert that animals have been fed in vain on the pulse, no morbid consequences

having followed. In other epidemics the domestic animals have suffered distinctly enough, sometimes before the disease was noted in men. Swine fed on the pulse become paralysed, and often show spasms: in an old herbal it is stated that these animals fed on the meal lost the use of their hind limbs but grew very fat. Sheep and cattle do not appear to be affected.

There can no longer be any doubt that lathyrism in horses may be induced by feeding them on lathyrus; and these cases are of much interest from a pathological point of view (57, 58). The horse presents a series of symptoms different from that of man, which may account for the discrepancy of the accounts of the susceptibility of animals. In the horse the heart and respiration are chiefly affected and the larynx especially; so that the animal stands with stretched-out neck striving against the asphyxia which soon destroys him. Often the horses appeared quite well when at rest, but during work they took to roaring, became dyspnœic and sometimes suddenly fell down dead. Changing the diet arrests the malady, and tracheotomy prevents the sudden death.

After death the mischief is found mainly in the cells of the anterior horns of the cord, which are diminished in number and atrophied; there is also thrombosis of the small arteries. The arteries are thickened. The heart presents signs of fatty change, and so likewise do the intrinsic muscles of the larynx.

If on careful repetition of these observations the results are found to be constant, and to be attributable to the pulse, they may indicate that the nervous mischief is not primary, but consequent upon vascular lesions. Thrombosis is mentioned in the accounts of the spinal lesions in man. If this be correct it would suggest a similarity of action between the lathyric and the ergotic poisoning, in the former of which, as we have seen, coagulations are formed in the smaller arteries.

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ALCOHOLISM

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In this article reference is first made to the physiological action of alcohol. A few remarks are then made on the various common alcoholic drinks. The phenomena of drunkenness and of acute alcoholic poisoning are briefly described. Chronic alcoholism is next dealt with; and, lastly, an account is given of delirium tremens.

Ethyl Alcohol (C_2H_5HO) is the member of the alcoholic series found in wines and good spirits. When alcohol is obtained directly from sugar ethyl alcohol is formed alone; but when indirectly, by transformation of starch into sugar, some amyl alcohol ($C_5H_{11}HO$) (in the fusel oil) always appears with it.

Absolute alcohol contains not less than 99 per cent by weight of

alcohol, and not more than 1 per cent of water, has a specific gravity 0·793 at 60° F., and boils at 78° C. (173·6° F.).

Rectified spirit contains 10 per cent of water. The Spirits (Strength Ascertainment) Act, 1818 (58 Geo. III. c. 25), defines "Proof Spirit" to be that which, at the temperature of 51° Fahrenheit, weighs $\frac{12}{13}$ parts of an equal measure of distilled water. A gallon of proof spirit contains, approximately, 50 per cent of alcohol by weight. (Spirit above "proof" when ignited fires gunpowder; spirit under proof does not.) Every additional 0·5 per cent of absolute alcohol above 0·92 is said to be one degree above proof (29). According to the American standard, proof spirit contains 42·7 per cent of alcohol by weight.

Physiological Action.—It is important to differentiate, if possible, between the purely physiological effects on the one hand, and the pathological effects on the other. From want of this, contradictory statements have been made as to the physiological effects of alcohol.

Metabolism.—Very divergent opinions have been expressed as to the effect of alcohol on metabolism, probably because it is difficult to draw a hard and fast line between the effect of very small amounts, which serve as food, and that of larger quantities, which act as a protoplasmic poison and diminish metabolism. Since it undergoes oxidation, alcohol protects the fats of the body from combustion; in fact Atwater found that it is practically as efficient in this respect as the fats and carbohydrates of food. The use of alcoholic drinks, especially of those containing sugar, such as beer and porter, leads to an increase in the amount of bodily fat; usually this increase is uniformly distributed over the body, but not invariably; thus the diffuse lipomas, the most marked examples of which are seen in the neck, have a definite relation to alcoholic excess. While it has now been shewn that alcohol is a proteid-sparer, it sometimes fails to have this action; it is not improbable that in persons unaccustomed to alcohol there is at first a temporary increase of the disintegration of proteid, but that the organism soon adapts itself to alcohol, so that the katabolic change of proteid ceases and the nutritive effect of alcohol comes into play. Though it is not absolutely proved, alcohol probably contributes its share to muscular work. Small quantities increase the output of work done for a time, but as the stimulating effect passes away the capacity for work falls considerably; its action thus consists in bringing out the reserve powers for a short effort, and not in restoring or husbanding sources of energy. The experience gained from long marches of troops is that the use of alcohol tends to diminish the total amount of work done. It may enable a man "to spurt," but not "to stay." It is dissipative rather than conservative of energy.

Digestive System.—In the mouth alcohol gives rise to a feeling of warmth and, reflexly, to a flow of saliva. In a similar manner it is thought that it may dilate the vessels of the brain, thereby stimulating it (Brunton). *In the stomach* the vessels become dilated and, reflexly, the secretion of the gastric juice is increased, with a rise in the amount of pepsin and hydrochloric acid. Alcohol, unlike water, is rapidly absorbed

from the stomach, and, reaching the stomach again through the blood-vessels, indirectly stimulates secretion. On the other hand, the presence of large amounts of alcohol retards gastric digestion; some wines, such as sherry, exert this inhibitory effect in virtue of their solid constituents and not of the contained alcohol. On the whole, it appears that in normal conditions, gastric digestion in its entirety may not be materially modified by the introduction of alcoholic fluids with the food (Chittenden). The presence of alcohol or of alcoholic liquors hinders artificial digestion.

Circulatory System.—Alcohol is rapidly absorbed unchanged into the blood, and may be detected there for several hours. It can pass from the maternal into the foetal blood. Experimentally, alcohol rapidly increases the viscosity of the blood, and so increases the work of the heart (Burton-Opitz). It diminishes phagocytosis. In healthy persons small doses of alcohol or of alcoholic drinks usually produce no alteration in the pulse-rate, provided that local irritation in the mouth and stomach and other factors, such as the effect of mental excitement and movement, are obviated. In the same circumstances alcohol has no effect on the heart and is not a circulatory stimulant; but, as the result of local irritation of the mucous membrane of the mouth and stomach, the heart may reflexly beat more forcibly and more rapidly, this is commonly believed to be the action of alcohol on the heart. As these effects pass off, the heart beats less powerfully and more slowly. It is often stated that there is a transient rise of blood-pressure, followed by a more prolonged fall, but it appears that in moderate amounts alcohol has no appreciable effect on arterial blood-pressure; when any change does occur, it is always in the direction of a fall, never of a rise. Large doses give rise to a fall, due to the depressing action of alcohol on the central nervous system and on the heart (Abel). The peripheral blood-vessels are usually dilated and thus the familiar flushing of the face is produced.

Temperature.—As a result of the dilatation of the peripheral vessels, and the large amount of blood passing through the cutaneous areas, the loss of heat by radiation and convection is greatly increased. This leads to a compensatory increased production of heat by the tissues; further, alcohol is oxidised and gives rise to heat-production, one gramme producing seven calories of heat. The outcome of the effect of alcohol is in the direction of lowering the temperature, and when large quantities are taken this may be extremely marked. But here again it is important to remember the distinction between the physiological and the toxic effects of alcohol. Atwater has shewn that, when given in such small doses that the vessels of the skin are not dilated, alcohol causes no considerable increase in the amount of heat radiated from the body.

Respiratory System.—Alcohol is a respiratory stimulant and increases the volume of air passing through the lungs and the absorption of oxygen; these effects are more readily produced by alcoholic beverages containing stimulating esters than by pure alcohol, and are more marked in tired than in normal persons. The increased absorption of oxygen is regarded by Singer as the response to the demand created by the increased oxidation-

processes in the tissues which compensate for the increased loss of heat. Contradictory statements have been made about the effect of alcohol on the output of carbonic acid gas, but it appears that, like ordinary food, it increases the amount exhaled.

Central Nervous System.—Alcohol has first of all an indirect effect; by its action on the circulation it supplies the brain and spinal cord with more blood and so should increase their activity: it acts, however, directly on the nerve-cells as a functional poison. After a small quantity of alcohol there is a subjective sensation of greater efficiency; but this is fallacious, and is due to failure of intellectual judgment. Kraepelin's experiments shew that the simple reaction-period is temporarily accelerated and then prolonged after alcohol; but that a complex reaction, in which an association of ideas is involved, is observed from the first. The action of alcohol on the higher centres is, therefore, depressing. The higher centres connected with mental activity suffer first; after the cerebrum the cerebellum and cord are affected, and last of all the automatic centres in the medulla controlling the vasomotor, respiratory, and cardiac movements become paralysed.

Physiological Amount.—The amount of alcohol which can be taken daily for long periods without producing any pathological results varies, of course, with the age, surrounding conditions, and idiosyncrasies of the individual. From experiments on soldiers Parkes and Wollowicz came to the conclusion that one and a half ounces of absolute alcohol was the physiological amount. But since then general opinion has come to regard one ounce as the limit for the average person. Great differences, however, exist in different individuals, and it would not be safe to regard even this amount as universally harmless.

Strictly speaking, alcohol must be considered as a food since it is oxidised and provides energy, but it is not a complete food as it does not build up or repair tissues; it is a very expensive form of food, and, most important of all, its toxic properties so far outweigh its nutritive value that for practical purposes it cannot rank with other foods. There is no doubt that healthy and young people are better without alcoholic drinks; even moderate amounts often lead to excess in the young. As age advances alcoholic beverages may be useful and the same is true with regard to disease, but not to the extent that is often practised even now.

Elimination of Alcohol.—Moderate amounts of alcohol are oxidised in the body in the same way as carbohydrates; from 95 to 98 per cent is used up in the body, and passes off as carbonic acid gas and water. Alcohol is rapidly absorbed unchanged from the alimentary canal so that none is found in the fæces. Binz estimated that of 2·9 per cent leaving the body 1·6 escaped by the lungs, 1·17 by the kidneys, and ·14 by the skin. Alcohol is a somewhat feeble diuretic, the marked effect of some liquors, such as gin, being due to other constituents.

ALCOHOL BY WEIGHT IN VARIOUS LIQUORS (FROM ATWATER)

	Range.	Average.		Range.	Average.
Wines.	per cent.	per cent.	*Spirits.*	per cent.	per cent.
Claret	6-12	10	Brandy, Cognac, from wine	40-60	47
German, Rhine, Moselle	7-12	8·6	Brandy from spirit	36-42	39
Port	16-18	17	Gin	20-40	30
Sherry	16-20	17·5	Whisky	36-43	40
Madeira	15-16	15·4	Rum	40-80	60
Marsala	11-24	16	*Liqueurs.*		
Malaga	9-14	12	Benedictine		38
Champagne	8-11	10	Chartreuse		32
Tokay	7-15	10	Curaçoa		42
			Absinthe		51

Alcoholic Liquors.—The effect of alcoholic beverages is partly due to the ethyl alcohol they contain, and partly to the presence of additional bodies. Sugar and dextrin may be useful as foods, while the esters (or compound ethers) and salts may be of use in furthering the processes of digestion; and again, other members of the alcoholic series—amyl, butyl, and propyl alcohols—furfurol, and definite adulterations, when present, may exert a decidedly toxic action; so that a dose of such a fluid may be more deleterious than the same amount of alcohol. The effects of alcoholic beverages do not therefore correspond exactly with those of alcohol. Alcoholic beverages may be considered as:—

(i.) Beer, porter, cider, etc.; (ii.) wines; (iii.) spirits; (iv.) liqueurs; and (v.) other alcoholic and allied liquids taken purely to produce intoxication.

(i.) *Beer, Porter, Cider, etc.*—English beer contains about 5 per cent by weight of alcohol, besides extractives, salt, sugar, dextrin, lactic acid, and lupulin, the active principle of hops. Lupulin exerts a depressing action on the nervous system, producing sleep. Stout and porter contain caramel, to which their colour is mainly due.

Sweet cider contains about 3 per cent of sugar, and readily undergoes fermentation, becoming changed into rough or hard cider. There is danger that during fermentation the process may go on to the production of acetic acid and render it sour. Sour cider may set up colic, diarrhœa, and intestinal disturbances. Cider contains malic acid; hence if it be allowed to act on lead some of the metal is dissolved: lead poisoning, as pointed out by Sir George Baker in 1767, may thus be set up. The good effects of cider in gout have been ascribed to the acid malates in it. Cider contains from 1 to 8 per cent by weight of alcohol. Perry, like cider, is allied to wine rather than to beer.

These liquors may give rise to dyspepsia, but not in nearly so marked a degree as the more concentrated spirits; with the exception of fully fermented or rough cider, they are undoubtedly a prolific source of gout.

Beer has been adulterated in many ways. Picric acid, strychnine, quassia, and chiretta have been used instead of the hop-bitters. Cocculus indicus, which contains the neutral principle picrotoxin, is probably added for the same reason. Opium, for its narcotic effects, salt, presumably to increase thirst, and salicylic acid, as a preservative, have been added. Arsenic may gain an entrance into beer in the process of its production and give rise to epidemic arsenical poisoning. In the outbreak of arsenical poisoning in beer-drinkers in the North of England and Midland Counties in 1900-1901, the sugars used in the process of brewing contained arsenic. It was shewn that the source of the arsenic was the sulphuric acid employed in the production of the sugars, and that it was made from the Spanish pyrites, which often contains a large percentage of arsenic [Reynolds].

(ii.) *Wines* are obtained from the fermented juice of the grape. When all the glucose becomes changed into alcohol the wine is called "dry"; if some sugar remain the wine is called sweet. The "body" of a wine depends on the amount and blending of the solids (sugar and extractives). By the term "bouquet" is meant the perfume to the nose; and by "aroma" the effect on the posterior nares when the wine is on the back of the tongue. The bouquet and aroma are both due to the compound ethers and aldehydes. The maturing of wine is the process of development of these ethers. Roughness is due to tannic acid, of which red wines contain far more than white.

Natural wines contain 5 to 14 per cent of alcohol; 14 per cent of alcohol in a solution stops the fermentation of sugar, so if a higher percentage of alcohol be found, it is due to the subsequent addition of alcohol. Wines, such as Port, Sherry, and Madeira, to which spirit has been added, are said to be fortified or brandied.

White wines are made from white grapes, or from red grapes the skins of which have not been left in the fermenting juice or "must"; in the case of red wines the skins of purple grapes remain in the must.

Sparkling wines have this quality in virtue of the carbonic acid, formed during fermentation, which is retained in them; as in Champagne and sparkling Hock. Some sugar is usually added to Champagne before it is finally bottled for the market.

The colouring matter of wines is precipitated in the crust; hence wines become lighter in colour on keeping.

Constituents of Wines.—After alcohol the most important factors in wines are the acids, the amount of sugar, and the ethers.

Wine contains some glycerin. The juice of the grape does not contain tannic acid, which is obtained from the skins and the pips. Malic and tartaric acids are found in the juice. Clarets, Bordeaux, and Hungarian wines contain tannic acid; Hocks, Moselle, and Chablis are acid from the presence of tartaric acid, and do not contain any tannic acid. In good wine the amount of acid should not exceed ·5 per cent. The acids act on the alcohol, and thus lead to the formation of ethers. Acid wines on keeping deposit a crust of acid tartrate of potassium, tannin, and colour-

ing matters which is at first copious; subsequently it becomes scanty, and then, when floating in the wine, is known as "beeswing." In addition to acid tartrate of potassium wine contains tartrates of sodium and calcium. In France red wine is frequently "plastered" by the addition of potassium sulphate, and Lancereaux suggested that this was an important factor in the production of hepatic cirrhosis. By the *loi griffe* (1901) the amount of sulphate of potash allowed to be added to wine was restricted to two grammes per litre.

In natural wines all the sugar may be transformed into alcohol, in fortified wines the added spirit checks fermentation, so that the sugar remains unchanged. Sweet or liqueur wines, such as Tokay, Malaga, Constantia, and Tent, contain a large amount (20 per cent) of sugar. Sometimes, on keeping, these wines become ropy from the sugar fermenting into a form of mucilage.

The following classification is Sir A. Garrod's:—(*a*) Spirituous wines, containing a considerable quantity of saccharine or unfermented matter, and an amount of alcohol, usually above 15 per cent by weight. The chief wines in this class are Port, Sherry, Madeira, Marsala; (*b*) Liqueur wines, containing much sugar—Tokay, Malaga, Tent, Constantia, etc., the higher Sauternes; percentage of alcohol between that of the 1st and 3rd classes; (*c*) Acidulous wines, rich in acid tartrate of potash; alcohol not much above 10 per cent. (*α*) With tannin and colouring matters—Clarets or red Bordeaux wines; red Burgundies and Hungarian wines. (*β*) Without tannin or colouring matters—Hocks, Moselle, Chablis, and the light dry Sauternes. (*d*) Effervescing wines, containing unfermented matter and free carbonic acid—Champagne, sparkling Hock, Moselle, and sparkling Burgundy.

(iii.) *Spirits.*—Whisky, gin, rum, and brandy contain alcohol in considerable amount, water, and the compound ethers to which their characteristics are due. There is a little sugar in gin, but none in the others. Spirits, from the large amount of alcohol in them, produce more marked dyspepsia than beer, but have much less tendency to set up gout.

While the concentration of the alcoholic drink is the important factor in the development of symptoms connected with the alimentary canal, the total amount of alcohol—whether it be taken as wine, beer, or spirits—is the important factor in determining nervous symptoms.

Whisky (sp. gravity ·915) contains about 40 per cent of alcohol. It is obtained from malted grain, usually barley, and contains some amyl alcohol, which is said—though on this point there is some difference of opinion—to disappear in the process of mellowing and to be converted into esters. It has recently been stated that the bad effects, such as headache, formerly ascribed to amyl alcohol are due to aldehydes, and especially to furfurol. Whisky should always be kept for at least two years to enable it to mellow and lose the unpleasant taste it has when new. During the process of keeping its alcoholic strength diminishes. Originally almost colourless, whisky gets its colour from the sherry or other casks in which it is stored. It may be adulterated with methyl alcohol,

creasote, etc.; and, besides causing gastritis, it has usually been credited with a special aptitude to produce cirrhosis of the liver.

Gin (Geneva), Schiedam, or Hollands, is obtained by distilling unmalted grain. It contains a somewhat varying amount of alcohol (20 to 40 per cent), and a little sugar. It is flavoured with oil of juniper, to which its diuretic action is due. Gin may be considered as a flavoured and rectified variety of whisky; it has much the same effect as whisky. It has been adulterated with sulphuric acid, zinc, lead, alum, and cayenne. When sweetened and diluted by the retailers gin is known as gin cordial or "Old Tom." Unlike whisky, brandy and rum, it does not improve by keeping.

Rum is made by fermenting molasses; its flavour is due to ethyl butyrate; it has an alcoholic strength of 40 to 80 per cent; its dark colour is due to burnt sugar.

Brandy varies in alcoholic strength from 40 to 60 per cent. Cognac and the better kinds of brandy are distilled from wine; ordinary brandy is, however, often obtained from malt. The flavour is due to ethers derived from the wine from which it is distilled. It obtains its colour from the oak casks in which it is stored, and sometimes from added caramel. It may be adulterated with methyl and amyl alcohols, salts of zinc, of lead, or of copper, salicylic acid, and cayenne. Brandy is supposed to be particularly apt to give rise to delirium tremens.

Arrack is the fermented juice of the cocoa-nut tree, palmyra, and other palms; common kinds are obtained from rice. The alcoholic strength is 52 per cent. Hindoos and Malays consume much of it. Indian hemp is sometimes put in to poison the drinker.

In Koumiss and Kefer, obtained from fermented mare's milk, a double fermentation—lactic and vinous—takes place. The amount of alcohol is less than 2 per cent.

(iv.) *Liqueurs* are strong spirits sweetened with sugar, flavoured with aromatic substances, and artificially coloured. Liqueurs of British manufacture are usually inferior, and are known as cordials. Bitters are a special kind of liqueur with tonic or medicinal properties. Gentian is the staple bitter.

Curaçoa is flavoured with orange peel; Kirschwasser and Maraschino with cherries. The flavour of Chartreuse is complex, but is chiefly due to balm leaves and tops.

Absinthe, of which there are several varieties, is a bitter liqueur and is not drunk neat, as are the other liqueurs, but well diluted with water. It contains, besides volatile oils such as cinnamon, cloves, peppermint, anise, and angelica, only 0·33 per cent of the oil of wormwood (*Artemisia absinthium*), which is responsible for its peculiar toxic effects, from 45 to 75 per cent of absolute alcohol, traces of chlorophyl, and sometimes sugar. It has a convulsive action, stimulating not only the cortex, thus giving rise to epilepsy, but also the centres in the medulla; according to Prof. Boyce the cord is not affected by absinthe.

Chronic Absinthism.—In these cases there are digestive disturbances,

thirst, emaciation, loss of hair, patches of cutaneous anæsthesia preceded by itching, tremor, giddiness, depression passing into melancholy or dementia, and, as already mentioned, epileptic fits which vary directly with the amount of the poison taken. "Absintheurs" suffer from hallucinations of hearing and sight quite apart from any condition like delirium tremens, and become utter wrecks physically and morally. The drug is chiefly drunk in Paris, where it was introduced after the Algerian war of 1844-7 by the soldiers who, when on service, had been advised to mix absinthe with their wine as a febrifuge.

(v.) *Other Alcoholic and Allied Liquids Employed to Produce Intoxication.*—Ether is occasionally taken to induce intoxication. [*Vide* p. 974.]

Women have recourse to tincture of lavender, eau-de-cologne, and even tooth-washes to satisfy their cravings for intoxication; and are thus enabled to drink secretly. Tincture of capsicum, which has often been employed medicinally to overcome drink-craving, has also itself been used to produce drunkenness. Jamaica ginger was so extensively consumed in Georgia (N. Kerr) that it has been scheduled there as an intoxicant. Its effects are said to be more depressing than those of alcohol alone.

Alcoholism

Etiology.—The causes of alcoholism may be divisible into the usual two headings:—(*a*) Disposing causes include the factors which are inherent in the individual himself, such as a special idiosyncrasy or susceptibility to alcohol due to hereditary causes, and also any acquired susceptibility such as may result from sun-stroke or injuries to the head. The influences exerted on the patient by his surroundings, profession, occupation, or trade are included under this head. Hereditary taint may be traced in a very large proportion of alcoholic cases—it is said in nearly a moiety. The children of drunkards are extremely susceptible to the influence of alcohol; a quantity that would not affect ordinary persons intoxicates them, and produces results not so readily seen in more normal persons. The craving for alcohol seems to be handed down to them, and they take to drink as a duck to water. It has been said that when the father has been a drunkard it is rather the moral nature of the offspring which is altered; when the taint is on the mother's side, that the brain and nerves are particularly liable to suffer: the mother's influence is said to be the more powerful of the two. Drunkenness not only breeds alcoholic tendencies but produces a decidedly neurotic taint and a disposition to insanity; conversely, the offspring of neurotic or insane parents may be particularly susceptible to the effects of alcohol. The influence of heredity, therefore, consists in an unstable condition of the nervous system, which may be due either to drunkenness or to disorder of the nervous system in the parents. Thus drunkards beget "neuropaths" or "degenerates," and neuropaths again may have drunken offspring. Drunkenness has been divided into (*a*) simple or acquired, and (*b*) complicated or patho-

logical; with the latter we are now dealing. The effect of alcohol is different in the two cases: a degenerate person suffers more severely and more rapidly. Thus, he is more likely to die of delirium tremens, while an ordinary drunkard lives on, and eventually perhaps dies of cirrhosis of the liver. Not only does the degenerate person become affected earlier, and in a greater degree, but the manifestations are somewhat different, and are especially connected with the nervous system. Instead of the classical intoxication, a maniacal, melancholic, or suicidal drunken fit follows a debauch. Delirium tremens is more frequent; its stages are more prolonged, and are manifested more gradually than in ordinary drinkers. Impulsive drunkenness or dipsomania is the result of an hereditary taint, though it may come on when instability and loss of inhibitory power in the nerve-cells of the cortex have been acquired; as, for instance, after sun-stroke or head injuries. Such a sufferer, however healthy the stock of which he comes, after a blow on the head or a sun-stroke may become extremely susceptible to alcohol; just as if he were the offspring of drunkards or neurotics. Of the two sexes, males are more often the subject of alcoholism than females. In the ten years ended 1904 the Registrar-General's returns for England and Wales shew that 26,426 persons died from alcoholism (including delirium tremens); of these 15,681, or 59·34 per cent, were males, and 10,745, or 40·66 per cent, females. During the same period the deaths from cirrhosis of the liver were 55·6 per cent males and 44·4 per cent females. The drink-habit almost always develops before the age of 35, and somewhat rarely after 50. Of the total deaths from alcoholism in 1904 in England and Wales 91 per cent, according to Dr. Tatham, occurred within "the working period of life," viz., from 25 to 65 years, whilst the proportion of deaths from other causes within the same limits of age did not exceed 31 per cent of the total at all ages.

The influence of occupation is well marked. The liquor traffic naturally is pre-eminent as a hot-bed of intemperance. Next, but long after, come trades necessitating exposure to severe weather—those of cabmen, drivers, night-watchmen, bargemen, and hawkers. Soldiers and domestic servants shew a considerable degree of intemperance. Sailors, partly from force of circumstance, partly perhaps that their outdoor life counteracts the evil results of alcoholic excess, are, as a class, either more temperate or less poisoned than soldiers. The church has the post of honour in the list; among the other professions the schoolmasters approach most nearly to the ministers of religion, then officers in the army and navy, then medical men, and then lawyers. Indoor occupations have been said to dispose to alcoholism from their dulness and monotony, and also because the effects of drink are not counteracted by active exercise in fresh air.

Apart from direct inheritance, the surroundings of the individual, convivial or miserable, and the example of his parents have a considerable influence, especially in the lower classes and in crowded populations. Race may be a factor of some importance. The Jews are very temperate;

possibly this, and the care they take in selecting their food, may account for their comparative freedom from tuberculosis. The inhabitants of cold or temperate countries are more addicted to alcoholic excesses than those of the tropical climates.

Increased prosperity of the country means an increased consumption of alcoholic liquors per head of the population; thus the consumption of beer per head, which was $24\frac{1}{4}$ Imperial gallons in 1861, and 29·7 in 1903, touched its highest point in 1874, a year of great prosperity, at 34 gallons. In wines and spirits together the consumption per head in 1861 was $6\frac{7}{8}$ pints, in 1875 $10\frac{1}{4}$ pints, and in 1903 $7\frac{7}{8}$ pints per head.

(*b*) Exciting causes.—Mental distress, loss of relations, friends, money, or reputation, drives many a sober man to the bottle. The desire to forget leads to much drinking, especially among women; and over-work, the desire to tide over a crisis, worry and its oft-accompanying sleeplessness, social gatherings, nay, even the wine of the Eucharist, may be the means of awakening a dormant taint or of sowing the seeds of the drink habit. Failing health, rheumatic or other pain, neuralgia, megrim, dyspepsia, menstrual troubles, or the disturbance of the menopause may act in the same way. Taken first as an anodyne, the habit grows and a definite craving becomes established. Chronic alcoholism has been developed in a total abstainer who was taking a patent tonic medicine which, unknown to him, contained alcohol (17). Sir Isambard Owen, from the data of the Collective Investigation Report, estimated that one in every three of the population is liable, under appropriate conditions, to develop this morbid taste. The craving is rather for the after-effects than for the æsthetic pleasure experienced by the palate: the taste of the drink itself, indeed, is to some drunkards positively offensive. The means employed may be pleasant or repulsive; expensive wines, raw spirits, or whatsoever comes to the hand.

The morphine, cocaine, and drink cravings are much alike; from its ubiquity alcohol is the means most commonly employed, and once adopted is continued.

Acute Alcoholism

Drunken Fit.—The ordinary phenomena of intoxication are too familiar to need much description. As with other poisons or drugs, there is no constancy in the dose of alcohol which produces distinct results, or in the character of these effects in different persons. In some persons a small amount will produce most marked and violent intoxication; this is especially the case when there is an hereditary "alcoholic taint." The nervous system being unstable needs but little of the noxious poison—for such it is in these cases—to disturb its balance and to precipitate a condition which might be compared to temporary insanity. In cases with a family history of insanity the influence of the taint may shew itself in maniacal excitement, in a suicidal or homicidal tendency, or in other imitations of recognised mental disease. This extreme susceptibility to the influence of alcohol may also depend on an

acquired condition of nervous instability, such as follows a blow on the head or a sun-stroke. Early in ordinary intoxication a want of self-control becomes evident, the silent man becomes confident and expansive, the habitually modest man boastful and egoistical; the restraint of reason is removed, and free play given to the expression of the feelings. As the clouding of the higher psychical centres concerned with thought, discrimination, and the control of the emotions advances, it spreads onwards to the motor areas; incoördination of ideas is succeeded by incoördination of speech and motion. Sometimes, however, the order may be reversed, and a person apparently sober so long as he is sitting down, may find on getting up that he is no longer master of his legs, and walks like a man with advanced locomotor ataxia. These effects of alcohol have been compared with those of advancing mental disease; general paralysis of the insane, with its progressive disintegration of the nervous system, being imitated by temporary intoxication. Dr. Maudsley describes drunkenness as a brief chronicle of the successive phases of insanity displayed in a short period of time. First there is a condition of stimulated energy with weakened self-control, like the mental excitement which often precedes mania; then follow motor and sensory disorders, incoherence of ideas, uncontrolled excitement or unreasoning melancholy; and, lastly, a condition of stupor which might be called temporary dementia.

When the full narcotic effect of alcohol has come about, the individual is, as it is commonly called, dead drunk. In this state of alcoholic coma the vasomotor centre is paralysed, and, as a result of this, injuries which would kill a sober man by shock have comparatively little effect on the drunkard.

Acute Alcoholic Poisoning.—When a large quantity of strong spirit is taken at once—as, for instance, when a bottle of whisky or brandy is drunk off for a wager—the effect may be so extreme that death rapidly follows.

Such an event, however, is rare: it more often happens, when a quantity of strong spirit is taken, that considerable collapse from the irritating effect of the poison on the stomach walls comes on; then, as absorption takes place, the patient gradually passes into a state of coma like that which results when a large quantity of alcohol is imbibed gradually. This coma is due to the narcotic action of alcohol on the nerve-cells of the cerebral hemispheres. The unconsciousness is of varying degree; generally the patient can be roused by persistently tapping the forehead or slapping the face, or by the application of the battery. The limbs are flaccid, but there is no difference between the two sides, as in hemiplegia; the skin may be flushed and somewhat cyanosed, but is usually cold; the pupils are equal and generally dilated. The pulse is full, and the breathing deep and sometimes stertorous. The breath has an alcoholic odour, but little stress should be laid on this, as cerebral hæmorrhage or epilepsy may, of course, come on after drinking; or opium or other narcotic poisons, such as chloral, may have been mixed

with the alcohol; or again, with the best intentions, friends or bystanders may have poured some stimulant into the patient's mouth after he began to be ill. Muscular twitching or general convulsions may occur, and these, if often repeated, may lead to the status epilepticus. If this occur the temperature may rise until death closes the scene, apparently from hyperpyrexia; still more rarely death, after an epileptic fit, may occur quite suddenly from syncope, with but little pyrexia. The occurrence of convulsions, however, is a comparatively infrequent event in acute alcoholic poisoning, the usual course being that of narcotic poisoning. The factors which in certain cases are responsible for these epileptic manifestations are—(*a*) The existence of ordinary epilepsy in the patient or of an hereditary taint; here drinking is one of many events which may precipitate an attack. (*b*) The convulsive action of certain alcoholic drinks; thus, absinthe and furfurol (which is found in spirit made from rye) give rise to a toxic epilepsy. Butyl and propyl alcohols have a similar convulsive action on animals, which ethyl or amyl alcohols do not possess.

It is the exception to find the temperature raised in alcoholic poisoning; as a rule it is depressed—sometimes to an extreme degree. If, however, the individual be inured to alcohol the depressing effect on the temperature is greatly diminished or absent. The coma may gradually deepen, and death from paralysis of the respiratory centre occur, or perhaps the patient may come round and then die somewhat suddenly. In the great majority of cases, however, appropriate treatment is followed by recovery.

Methyl or wood alcohol produces intoxication similar to that of ethyl alcohol, but the onset is slow and its duration remarkably prolonged—even for three or four days. Amblyopia may follow a single debauch; changes occur in the nerve-cells of the retina and in the optic nerve, and have been referred to the action of formic acid produced by the oxidation of methyl alcohol in the body.

Diagnosis.—With a clear account of the event there may be little doubt; but more often the diagnosis is one of probability only, and not infrequently it is impossible to be absolutely sure of the cause of coma in a person found in this state. In such circumstances the patient should be kept under careful supervision, and not left to sleep off a supposed drunken fit which may eventually turn out to be a state due to gross cerebral lesion.

Alcoholic coma may have to be diagnosed from post-epileptic states, from fracture of the skull, from intracranial hæmorrhage, from poisoning by narcotic poisons, and from the toxæmic coma of diabetes or of uræmia.

In distinguishing alcoholic coma from post-epileptic stupor the history and the condition of the tongue (whether bitten or not) will help. In cases where drinking has brought on an attack in an epileptic subject, the condition is one of epilepsy, and not necessarily of alcoholic poisoning—since a small amount of stimulant may produce this result; and the treatment should be directed accordingly.

Fractures of the skull may of course complicate drunkenness, and the coma may be due to depressed bone or meningeal hæmorrhage.

In cerebral hæmorrhage and in pontine hæmorrhage, pin-point pupils are usually present; the breathing is generally stertorous, but too much stress must not be laid on this, as it depends more upon the dorsal position than on the cause. If doubt still exist it is wisest to wash the stomach out, and then treat the case as one of cerebral hæmorrhage. Even if the contents of the stomach smell of alcohol there may still be an intracranial lesion, since the excitement of a stimulant may be the immediate cause of cerebral hæmorrhage. The bladder if full should be emptied, as some information may be derived from examination of the urine. The presence of alcohol in the urine would point to the ingestion of a large quantity, and to the strong probability that the case is one of alcoholic poisoning. A considerable amount of albumin or sugar would suggest uræmic or diabetic coma; but small quantities of either may be the result of intracranial lesions, and must not be confidently relied upon to indicate the cause of the symptoms.

Treatment.—In an ordinary case of drunkenness no special treatment is required; but when there is much stupor, or when coma is imminent, the stomach should be washed out by means of a soft rubber tube and funnel, and the patient roused by the application of the battery, or slapping with wet towels. When sufficiently awake, strong coffee may be given, and the patient put into a warm bed. Any signs of collapse must be treated by hot applications, friction, and, if need be, by a hypodermic injection of liquor strychninæ or ether.

Violent delirium or maniacal excitement may be rapidly subdued by the hypodermic injection of apomorphine, which is followed by vomiting and also by very considerable prostration. Convulsions, if recurrent, may be treated by the careful inhalation of chloroform, and the rare but dangerous pyrexia by the cold pack. As recovery proceeds gastritis will require appropriate treatment, which may with advantage begin with a sharp purge.

Morbid Anatomy.—Congestion and acute inflammation of the stomach, which result from the irritating effect of strong spirit, may go on to a superficial ulceration, but it does not usually pass beyond the catarrhal stage in which the mucous membrane is covered with ropy mucus. The intestines and œsophagus have been described as shewing a capillary injection of a bright red colour.

Hæmorrhages in the brain and lungs have been found in some cases. The brain has been described as having a distinctly alcoholic odour, but this is certainly not present in all cases. As shewn by animal experiments, alcoholic poisoning produces alterations in the nerve-cells, the protoplasmic processes of which undergo the moniliform change, while chromatolysis or disappearance of the Nissl granules occurs in the cell-bodies. These changes are not special to alcoholic intoxication since they occur in other conditions.

Chronic Alcoholism

Chronic alcoholism is the condition which results from the toxic effects of long-continued alcoholic excesses on all the organs and tissues of the body, but especially on the nervous and digestive systems. It does not include the results of alcoholic excess when focussed on particular organs—such as dementia, peripheral neuritis, or cirrhosis—but is the aggregate of the symptoms resulting from the earlier or preliminary stages of these and other morbid changes. The constant action of the poison leads to the establishment first of functional and later of structural alterations. The functional and metabolic changes induced in the first instance by the toxic action of alcoholic beverages lead to a secondary auto-intoxication, so that the disease known as chronic alcoholism is the outcome of these closely related factors.

From the continued activity of the temperance movement, and from the general belief that drinking habits, at any rate in the upper and middle classes, are much less than in past time, it might naturally be expected that alcoholism would be less frequent. Data for determining this point are difficult to obtain; in so far as the death-rate from intemperance is an index of the existing frequency of alcoholism, this is not the case; indeed, until the end of the last century, the reverse held good. The Registrar-General's returns shew that the death-rate from alcoholism for the quinquennial periods since 1866 steadily increased from 35·4 to 85·8 per million living in the quinquennium 1896-1900. Since then there has been a fall, thus, though the death-rate per million living in 1901 was 96, it stood at 84, 76, 70 for the years 1902, 1903, 1904. The death-rate from cirrhosis of the liver, which is closely connected with that of alcoholism, during the same periods advanced from 41·9 (in 1866-70) to 134·6 (in 1896-1900), and has fallen to 117 per million living both in 1903 and 1904. Dr. Tatham points out that while these figures justify the hope that there has at any rate been no increase in the loss of life due to intemperance, it would be rash to assume a substantial improvement in this direction until the fall in the fatality of those diseases that are most obviously associated with this habit shall have become more pronounced than is at present the case. The official returns shew that the consumption of alcoholic drinks per head of the population in the United Kingdom has increased since 1856; in that year 22·6 imperial gallons of beer and 1·26 gallons of wine and spirits were consumed per head of the population: in 1903 the amounts were 29·7 gallons and 1·32 gallons. In years of prosperity such as 1874, when 34 gallons of beer represented the consumption per head, and 1875, when 1·81 gallons of wine and spirits were taken, the amounts were much higher.

So far as statistics go, therefore, and they must not be pressed too far, there is reason to fear that alcoholism, although it appears to be diminished in some walks of life, is not really less frequent in one way or another than formerly. Secret drinking may have increased, or the

frequent use of "nips," which does not bring about the grosser forms of drunkenness. The increase of wealth and luxury no doubt leads to a large use of alcohol as an element of "good living.' On the other hand, the diminution of ordinary drinking is plain not only to every housekeeper and to every magistrate but also to the breweries.

Morbid Anatomy.—The action of alcohol as a protoplasmic poison is of paramount importance and is directly or indirectly responsible for the numerous morbid changes found in the organs and tissues of chronic alcoholics. As mentioned elsewhere, some of the changes are directly due to the toxic action of alcohol, while others are the outcome of auto-intoxication set up by alcohol. The changes are very varied, few, if any, are special to alcoholism and only a small number may be present at the same time.

The Alimentary Canal.—Chronic congestion and catarrh of the pharynx and pharyngitis are commonly met with. Chronic œsophagitis has been attributed to alcoholic excess, and it has been thought that dilatation of the veins at the lower end of the œsophagus may be due to alcohol even in the absence of portal obstruction and cirrhosis.

Alcoholism is a frequent cause of chronic gastritis; the mucous membrane becomes thickened and fibrosed, and shews scattered areas of pigmentation, more especially in the region of the pylorus, due to chronic congestion. The gastric glands undergo degenerative changes, and eventually atrophy. In beer-drinkers the stomach may be greatly dilated. Acute gastritis or, in rare cases, purulent gastritis may be produced by infection supervening in an organ, the resistance of which has been reduced by alcohol. Oral sepsis is often an important factor in these cases.

Chronic congestion leading on to catarrh is common in the intestines, but there are no very manifest naked-eye lesions in the intestines directly due to alcoholism. Piles, due to former constipation, may be made to bleed, and may become extremely irritable after alcohol has been taken.

Chronic pancreatitis with or without hepatic cirrhosis, may be caused by alcoholism. It is probable that duodenal catarrh may spread into the pancreatic duct and so set up chronic inflammatory changes in the gland. There is reason to believe that alcoholism commonly induces glycosuria and may cause diabetes.

Liver.—The common change found in the liver in chronic alcoholism is a deposition of fat in the hepatic cells which may lead to considerable enlargement of the organ. The change formerly spoken of as fatty degeneration is probably a pathological fatty infiltration brought about by toxic action, the vitality of the cells being lowered and deposition of fat thus favoured. The most striking change in the liver of chronic alcoholics is multilobular or portal cirrhosis. The rare hypertrophic biliary cirrhosis or Hanot's disease has no special relation to alcoholism. From the failure to produce hepatic cirrhosis in animals by the administration of alcohol it appears that alcohol is responsible for cirrhosis in an indirect fashion, namely, by setting up gastro-enteritis which gives rise to poisons possessing

a sclerogenic effect on the liver. Cirrhosis of the liver far more often follows alcoholic excess than any other factor. But it is noteworthy that, although alcohol is the main antecedent of cirrhosis, it is by no means so common for cirrhosis to occur in the course of chronic alcoholism. Thus, Formad in 250 post-mortems on confirmed drunkards, who had died suddenly from the effect of alcohol, found cirrhosis in six only, and concluded from this that alcohol does not produce cirrhosis. Further, it is remarkable how rare cirrhosis is in women with well-marked alcoholic neuritis. Possibly the contrast between the frequency with which alcoholism figures in the history of cirrhosis, and the percentage of cirrhosis in confirmed drunkards, may be explained by supposing that when the liver is susceptible and likely to suffer from the action of alcohol, it becomes affected comparatively quickly; so that, before the clinical picture of chronic alcoholism has had time to be completed, the symptoms of hepatic cirrhosis become clearly outlined. The statement that cirrhosis may follow prolonged exposure to alcoholic fumes apart from any consumption of the liquor is very difficult to prove.

It has generally been supposed that the production of inflammatory changes in the connective tissue of the portal canals, leads to the formation of new fibrous tissue which compresses and produces atrophy of the liver-cells. It is probable, however, that the morbid processes in cirrhosis are not limited to the formation of inflammatory tissue, but that changes in the hepatic cells and proliferation of the interstitial connective tissue occur simultaneously, and are due to the same cause. The view that degeneration in the cellular or active part of the organ is, as in alcoholic neuritis, the all-important factor, and that the fibrosis is a passive overgrowth, or of the nature of the fibrous substitution that occurs in old age in some organs, has been put forward; but it does not seem to be borne out by the histological appearances, which undoubtedly shew an active formation of young connective tissue. From the direct action of alcohol on the cells, however, degenerative changes result. Thus extensive fatty change may be found in the liver cells in cirrhosis and a large liver is produced. Not all large cirrhotic livers, however, owe their size to fat; many are large in virtue of compensatory hyperplasia of the hepatic cells.

Hepatic cirrhosis is very frequently associated with tuberculosis elsewhere. Thus in 706 cases of cirrhosis there was evidence of tuberculosis in 209 or 29·6 per cent (35), while in 75 cases of tuberculosis in alcoholic subjects there was cirrhosis in 46 or 60 per cent (Mackenzie). It is probable that alcoholic cirrhosis is less frequent in persons who lead an active out-door existence.

Acute red atrophy (a further stage of acute yellow atrophy of the liver) has in rare instances been found after excessive alcoholism; probably the action of alcohol as a protoplasmic poison reduces the resistance of the organ and so enables the actual cause of acute atrophy to become active.

Kidneys.—In heavy beer-drinkers the kidneys are commonly large

and hypertrophied but shew no morbid change; it is indeed a compensatory process analogous to that seen in diabetes. The amount of alcohol traversing the kidneys is probably small compared with that which passes through the liver. Since, however, it is a tissue poison the delicate renal epithelium in common with the brain and nerves, must suffer from its toxic action, as shewn by transitory albuminuria following excessive drinking. Some degree of fatty change in the renal epithelium is common in drunkards. There is considerable difference of opinion as to the influence of alcoholism on the production of granular kidneys; some statistics are opposed to the view that alcoholism is a factor in the causation of the disease. Thus Dr. Dickinson (11) found granular kidneys nearly in the same proportion in two series of 149 patients, one series being made up of patients who were connected with the liquor traffic, and so presumably drinkers, and the other series composed of persons who were not drunkards, or brought in contact in any especial way with alcohol. Formad, in 250 sudden deaths occurring in confirmed drinkers, found Bright's disease in 25, and concluded from this that there is no causal relation between drinking and kidney disease. It is, of course, possible that hard drinkers are enabled to carry on the practice in virtue of a comparative general immunity to the toxic action of alcohol; and the fact that Formad only found cirrhosis of the liver six times in his cases supports this hypothesis. That confirmed drunkards do not shew signs of kidney disease does not necessarily prove that alcohol may not affect the kidneys in more susceptible persons; the toxic results in such cases might be so marked as to prevent the individual from drinking to excess. It has been alleged that alcoholism affects the kidneys indirectly—that it first leads to gout and arterial change, and so to the kidney of arteriosclerosis. Prof. Welch sums up that the weight of authority and evidence supports the view that excessive indulgence in alcoholic liquors, fermented as well as distilled, is an important cause of chronic Bright's disease, especially of the small, granular kidney.

Respiratory Organs—Alcohol is excreted by the lungs to some extent. The direct toxic action exerted by it on the mucous membrane is probably the cause of the bronchial catarrh which is not uncommon in drinkers.

Chronic laryngitis, with thickening and opacity of the mucosa, which becomes like the epidermis (pachydermia laryngis), may occur in drunkards.

The old notion that alcoholism is protective against the development of tuberculosis is the reverse of the truth. Dr. H. Mackenzie, in 67 cases of pulmonary tuberculosis occurring in drinkers, found a family history of tubercle in 10 only. Since a family history of the disease is present in about 30 per cent of the ordinary cases, the effect of alcohol in producing pulmonary tuberculosis is considerable. Pulmonary tuberculosis of an active type is very frequent in peripheral neuritis of alcholic origin, and has been regarded as "trophic," and due to changes in the vagi. Such a factor may have had some share in the result; but the

generally debilitating influence of alcoholism is probably more important. With other forms of peripheral neuritis, except the leprotic, pulmonary tuberculosis is not often coincident.

Tubercles in the lungs are frequently found after death in cases of cirrhosis of the liver, which in the great majority of instances follows alcoholic excess. In 584 cases of cirrhosis tuberculous lesions in the lungs occurred in 22·6 per cent (35). Of Dr. H. Mackenzie's cases of tuberculosis in heavy drinkers there was cirrhosis of the liver in more than one-half; in 100 consecutive cases of fatal pulmonary tuberculosis occurring in persons over 20 years of age, in four years at St. George's Hospital, cirrhosis of the liver in any degree was present but 12 times. In his cases of alcoholic pulmonary tuberculosis Dr. H. Mackenzie observed excavation with bronchopneumonic consolidation and grey tubercles. The cases ran a rapid course, and fibroid tubercle was comparatively rare; but it must be remembered that these were clinically cases of tuberculosis, and this observation does not clash with the rule that very chronic pulmonary tuberculosis is commonly present in the bodies of drinkers.

Nervous System.—There is no specific lesion of the *brain* in chronic alcoholism, and in many drunkards there is no recognisable cerebral change. It is probable that alcohol does not act directly on the neural elements, but by disturbing metabolism leads to auto-intoxication and the production of toxins which cause the morbid changes. Thickening of the pia mater and arachnoid, increase in size of the Pacchionian bodies, and excess of the subarachnoid fluid due to atrophy of the brain, are common in alcoholic subjects, but are also normally found in old persons. In some cases the condition variously described as "pachymeningitis hæmorrhagica interna," "cyst of the arachnoid," or "subdural membrane," has been found; and not infrequently there are signs of chronic meningitis, such as thickening of the pia mater and adhesion to the underlying cortex. The brain is shrunken, and the convolutions distinctly separated by the sulci. The ependyma of the ventricles has been described as granular or villous, as in general paralysis of the insane. Microscopically the vessels passing in from the pia mater, and those in the brain substance, are tortuous, fibrosed, and may shew hyaline change and miliary aneurysms. The perivascular lymph-spaces are dilated.

There may be sclerosis from hyperplasia of the neuroglia, diminution in the number, degenerative changes, and pigmentation of the nerve-cells in the superficial and other layers of the cortex. The ganglion-cells may be swollen, vacuolated, and shew an absence of the Nissl granules or chromatolysis, and an eccentric position of the nucleus (*vide* fig. 7, pl. vi. vol. i.).

Chronic myelitis, probably due to meningitis and not shewing any systemic arrangement, may occur as the result of injuries so slight that but for the accessory element of alcoholism no change would have occurred in the cord (16). The condition may be associated with neuritis, but is independent of it. Degenerative changes in the cells in the anterior

cornua may occur, as in other kinds of peripheral neuritis, from interruption of the axis-cylinder processes of the cells. Systemic scleroses in the cord are occasionally seen, and when in the ascending tracts might be attributed to neuritis or an extension of the same process. Bevan Lewis, however, considers this by no means probable, and says the cord changes are due to slowly encroaching sclerous changes spreading from the membranes and creeping along the vascular tracts, especially along the posterior median raphe.

Nerves.—Optic neuritis in alcoholic subjects may be due to chronic meningitis. Two lesions have been described, retro-bulbar interstitial neuritis and atrophy of the nerve-fibres.

The changes on the nerves begin near their peripheral distribution, especially in the intramuscular branches of the motor nerves. First at one or more spots on a nerve-fibre the medullary sheath disappears entirely, the remainder of the sheath above and below this interruption still staining with osmic acid; the axis-cylinder in the affected part becomes attenuated and finally ruptures. The part of the nerve-fibre between the rupture and the muscle now undergoes Wallerian degeneration (S. Martin). The process is, therefore, primarily one of peripheral nerve poisoning and degeneration, and not of neuritis in the ordinary acceptance of that term. Severe neuritis may come on or be, so to speak, precipitated in an alcoholic subject as the result of some infection or other intoxication.

The degenerative effects of alcohol appear more rapidly in the peripheral than in the central nervous system. Recovery occurs in peripheral neuritis, unless the secondary degenerative changes in the corresponding nerve-cells have progressed too far.

Heart.—There is commonly excess of the epicardial fat and some fatty infiltration of the heart-walls, which may seriously embarrass its action. Fatty change in the myocardium is the most important effect produced by alcohol and leads to dilatation and in some instances to sudden and fatal syncope. In many cases, however, there are no definite histological changes; some cases shew interstitial myocarditis or patches of fibrosis (Aufrecht), but they are certainly not constant and are probably due to coronary disease. Moreover the direct action of alcohol on the heart-muscle enfeebles its contractile power and so leads to dilatation. The alcoholic heart is dilated, presents compensatory hypertrophy, and may weigh as much as 24 oz. In most cases the left side of the heart is first and mainly affected, but in some cases the chief change is dilatation of the right ventricle (Dreschfeld).

The alcoholic heart resembles a dilated heart due to chronic interstitial nephritis, though the kidneys only shew the effects of chronic venous engorgement or of compensatory hypertrophy. The association of cardiac kidneys and renal heart has often proved a stumbling-block. Sclerotic changes in the valves of the heart in alcoholic patients are often regarded as the result of the toxic action of alcohol; thus Prof. Osler accepts this explanation of some cases of aortic reflux. The dilated and hypertrophied

hearts (Munich or Tübingen beer-hearts) of those accustomed to drink beer in excess may be explained by supposing that at first there is compensatory hypertrophy in order to deal with the increased volume of blood and possibly with its increased viscosity, and that eventually this compensatory mechanism breaks down.

Arteries and Veins.—Alcohol is usually said to produce arteriosclerosis, but this has been disputed by Cabot. That alcohol may act as a tissue-poison on the vessel-walls cannot be denied; on the other hand alcoholism is frequently combined with other factors responsible for arteriosclerosis, and may further their effects; thus alcoholism favours the onset of syphilitic arteritis. It is more likely that alcohol is an indirect factor in the genesis of arteriosclerosis, and that as the result of the disturbances of metabolism and gastro-enteritis induced by it, toxic bodies are produced which set up endarteritis. Chronic endarteritis of the aorta may spread to the aortic valves and produce incompetency.

Indirectly alcoholism produces changes in the veins: thus cardiac failure and the resulting chronic venous engorgement lead to dilated and varicose veins, gout to thrombosis, and dyspepsia and cirrhosis to venous stigmata and acne rosacea about the face.

The Generative Organs.—The testes have been described as much atrophied in drunkards, but this event is very exceptional, and may have been an accidental association. Lancereaux has described an alteration in the seminal tubes of the nature of a premature senile change. Chronic alcoholism diminishes the fertility of both sexes, and leads to a stunted and ill-developed offspring, and so plays a most important part in infant mortality and racial degeneration. In women it has been thought that this is brought about by interstitial changes and fibrosis of the ovaries.

The Skin may become very smooth, waxy-looking, and extremely soft to the touch; this is partly due to the accumulation of fat under the skin, and partly to atrophy of the skin. General obesity is common, especially in beer-drinkers who almost exclusively supply the victims of diffuse lipoma.

The Muscles of the body appear flabby and somewhat fatty. In peripheral neuritis Dr. Sharkey (30) has described active inflammatory changes occurring in the paralysed muscles.

Bones and Joints.—The bones, like the rest of the body, are said to shew an increase in the amount of fat. Alcoholic drinks have no influence on arthritis deformans. By producing the metabolic disturbances resulting in gout, alcohol affects the joints in a marked though indirect way. The stronger wines—Port, Sherry, Madeira—and heavy beer and porter are most powerful gout-inducing agents. Burgundy is very badly borne by gouty patients. Champagne differs in its effects, the dry brands being less harmful than the sweet. Claret, Hock, Moselle and the lighter forms of malt liquors have comparatively slight gout-producing tendencies. Sir A. Garrod says that neither the acid, the sugar, nor any known principle in alcoholic drinks can be shewn to be the active factor in producing gout.

Symptoms of the onset are gradual, and the patient probably does not seek medical advice until the malady is fairly well established.

In the early stages there is a disinclination to work and a general want of energy; so that, although routine occupation may be got through, it is not well done, and any additional exertion—physical or mental—is avoided. This malaise is succeeded by headache, low spirits, and a pervading sense of impending misfortune. The mental powers are weakened; there is indecision even in matters of little or no importance, irritability, and want of self-control: sleep fails, or is unrefreshing, and the condition is often that of neurasthenia. Tremor, an early symptom, becomes manifest in the hands, lips and tongue. Anstie says that this tremor first occurs in the feet, and is worse in the morning, being chiefly due to the exhaustion of insomnia, and not entirely to the toxic effect of alcohol. To a certain extent, in the early stages, the tremor can be controlled by an effort of will; it is fine, and is brought out by any muscular effort, especially by an effort requiring precision or some slight manipulative skill. A sudden noise, such as the banging of a door, may make the patient tremble and perspire. There is, indeed, a general condition of jumpiness and nervousness—signs of a disordered cerebral function. The tremor is perhaps the first thing to attract the patient's attention, and to stop it he has recourse to an early morning dram; but food has a similar effect. These early symptoms persist and become more marked as the disease advances.

In a well-developed case the features are probably flabby, and the face often shews signs of chronic venous stasis; on the nose this may pass into the familiar acne rosacea, well described by Trousseau, and still popularly regarded as "the indelible stigma of drunkenness." The inference is, however, by no means necessarily correct; it may occur in uterine disturbance and in gastric catarrh due to causes other than alcohol. There is often some injection and slight œdema of the conjunctiva, and an icteric tint may be seen over the sclerotics. The skin of the body generally is smooth, soft, easily perspiring, usually pale, or even waxy. Extreme vasomotor excitability and a tendency to dermographism may be present, and pruritus, acne, and eczema be induced by periodic excesses. Alcoholism may set up a hæmorrhagic tendency. The tongue is usually, though not invariably, flabby and furred, and trembles when protruded; in women, however, the tongue is often clean, or it may be bare of epithelium. Superficial glossitis or leucoplakia may be found, especially in male alcoholics. The breath is foul, even apart from dyspepsia, and often has a peculiar heavy odour readily recognised by experienced observers; the mouth and throat are dry, and thirst is frequent. Pharyngitis and laryngitis of a chronic character are often met with, and lead to frequent hawking of phlegm and to some alteration of the voice. Want of appetite and indifference to food may pass into a positive loathing, so that very little nourishment is swallowed other than that which is contained in the alcoholic drinks. Like the other symptoms, the anorexia is worse in the morning; no

breakfast is eaten, and a state of exhaustion follows, which drives its victim to seek support and relief in spirits or beer. This want of appetite is aggravated by morning nausea and sickness due to gastritis: a small quantity of yellow mucus is usually brought up, and the same condition of catarrh spreads, though in a less marked degree, to the intestines, and gives rise to the looseness of the bowels, which is a tell-tale symptom; a capricious state of the intestines, in which constipation and diarrhœa alternate, is not uncommon. The gastro-intestinal symptoms vary considerably in intensity. Strong spirits are the most potent factors in the production of dyspepsia. Neat spirit is much more effective than larger quantities well diluted, inasmuch as its irritating action is more concentrated on the mucous membrane of the stomach. Occasionally the catarrhal gastritis of chronic drinkers may, as the result of a debauch, become quickened into an acute attack, and hæmatemesis may occur without any evidence, either at the time or subsequently, of hepatic cirrhosis.

Large draughts of beer may produce dilatation of the stomach and its accompanying symptoms. The liver in such cases is often tender and enlarged; a condition which may be due either to the early stages of cirrhosis, or to cardiac failure and consequent chronic venous engorgement. There are various forms of the alcoholic heart; there may be acute dilatation with a rapid and irregular pulse; in the chronic forms there are signs of dilatation with varying degrees of compensatory hypertrophy, breathlessness, general or widespread œdema, and other evidences of backward pressure. A rather special form of alcoholic heart in beer-drinkers, especially when the quantities taken are enormous, has been described as the Tübingen or Munich beer-heart. The alcoholic heart is often regarded as secondary to valvular disease or to arteriosclerosis, as the clinical manifestations are much the same.

In women sterility often results. Although every variety of menstrual disorder may occur, menorrhagia is the most common, and is possibly due to endometritis of the body of the uterus.

Insomnia, which may have been present throughout, becomes worse, and is accompanied by nightmares and dreams of a terrifying and distressing character. In the dozing state between sleeping and waking startling hallucinations of sight or of hearing may further disturb the patient. They correspond to the *muscæ volitantes*—mists and clouds before the eyes—noises in the ears, and giddiness experienced in the daytime. In rare instances toxic amblyopia due to alcohol, or perhaps to its action combined with that of tobacco, has been described; there may also be a central scotoma for red, green, and to a less extent for blue. Various peripheral sensations, numbness, tingling and cramps, or pain of a lancinating character, which appears to be neuralgic and gouty rather than the result of definite neuritis, may be met with; also starting and jumping of limbs, worse at night. The early symptoms of alcoholic peripheral neuritis are, of course, frequently present, but are not sufficiently conspicuous to stand out from the more general collection of symptoms

known as chronic alcoholism. Muscular tenderness, especially in the legs, alteration and impairment of sensation, pain, wasting and paresis of muscles, especially the extensors of the foot, leading to foot-drop, œdema, and loss of knee-jerk, may all occur and leave no doubt as to the existence of the lesions described under peripheral neuritis. [*Vide* article, vol. vi.] Alcoholic neuritis begins and is best marked in the legs, affecting the extensors especially; but subsequently it spreads widely. It is rare for it to attack the cranial nerves in an isolated fashion; but in severe cases the vagus is probably not uncommonly affected, and may be responsible for cardiac disturbance and failure; possibly some cases of facial paralysis are alcoholic in origin, though unrecognised as such. Alcoholic neuritis is much commoner in women than in men, and often follows quiet and secret, though persistent, drinking.

As the restlessness and nervousness grow worse, the depression of spirits may be so severe as to lead to suicidal attempts, or eventually to pass into melancholia. Want of will-power and lack of self-control are associated with failure in the memory, and form prominent features in the mental state of chronic alcoholism. The natural feelings undergo alteration; distrust and dislike supplant affection for members of the family; an anti-social attitude to mankind in general develops; and loss of proper self-respect is shewn by slovenliness, want of personal cleanliness, and a willingness to subsist on the support of others. There is a great alteration in the manner in which the items of the past and of the environment generally are regarded. In psychosis polyneuritica (or Korsakoff's syndrome), usually seen in women, there is, in addition to alcoholic peripheral neuritis, a state of mental confusion, described by Jackson and Sir S. Wilks, in which the patients lose account of time and place, seem to live in a strange world of their own, and will describe in detail events that are real to no one else. A less marked form of this want of correlation with the outside world makes the chronic alcoholic absolutely untrustworthy and apparently a purposeless liar of the most unblushing kind.

Not only are the mental and the intellectual processes impaired, but there is blunting of the moral sense, so that falsehood and deceit, especially where indulgence in drink is concerned, become habitual and shameless. This is very commonly seen in women drinkers; and in men the loss of even these shreds of self-respect is shewn in the cynical candour, albeit somewhat untruthful, with which they admit their past excesses, while, at the same time, they insist upon the recent reformation which, you must know, has come over their life.

The monotony of the course of chronic alcoholism may be varied from time to time by delirium tremens, or the local effects in some one tissue or organ may become predominant, and throw the general symptoms into the shade; so that the case now appears as one of cirrhosis, cardiac failure, peripheral neuritis, now passes into alcoholic dementia or other forms of definite mental disease.

Chronic alcoholism weakens the resistance of the body generally, and

favours microbic invasion. It disposes to the occurrence of various acute pyogenetic infections as is well shewn in the incidence of tropical abscess of the liver in drinkers as compared with abstainers. The influence of alcoholism in the etiology of pulmonary and peritoneal tuberculosis is equally undoubted. Experiments on animals fully confirm these clinical observations. It is notorious how badly alcoholics bear acute disease or injury. Thus, pneumonia is generally admitted to be very fatal in drunkards, and its occurrence, or indeed, any other serious accident, such as a broken limb, is frequently associated with delirium. Alcoholism facilitates the toxic effects of plumbism and the manifestations of syphilis.

The prognosis of chronic alcoholism is not very hopeful. The craving for drink is extremely hard to eradicate; and, though it may be kept in abeyance for months or years, there is always the danger that it will reassert itself when sudden strain or trouble arises. The difficulty lies rather in reformation than in cure of its results. The dyspepsia, tremor, sleeplessness, and so forth, can be alleviated with comparative ease so long as the patient is deprived of alcohol.

The occurrence of epilepsy is of bad omen. The influence of alcoholism in the production of insanity is very difficult to estimate since intemperance is frequently as much the effect of mental weakness as its cause; in the fifty-ninth report of the commissioners in lunacy intemperance was an assigned cause of insanity in 22·7 per cent of the male admissions, and 9·4 per cent of the female. The prognosis will, of course, be much more serious in a long-standing case, and in peripheral neuritis when the polyneuritic psychosis (Korsakoff's syndrome) is present. When organic change has taken place in the brain, and dementia has resulted, recovery is highly improbable. However, in some cases of chronic alcoholism, even though structural change be present, the outlook is not so gloomy. Thus, in peripheral neuritis recovery is frequent. In cirrhosis of the liver the process may be arrested and compensatory changes may lead to a condition of latency and very fair health. On the whole, much depends on the form of treatment. The immediate symptoms of the habit can usually be satisfactorily overcome; but a permanent and complete recovery is a matter of anxiety and uncertainty, and no case can be considered cured until at least two years have elapsed without any relapse into the habit. It is often stated that reformation of female inebriates is impossible and hopeless; but speaking with an experience of 20 years Dr. Branthwaite, the inspector under the Inebriates Acts, 1879-1900, is emphatically of opinion that "with equal consideration and treatment, women are every whit as reformable as men and possibly even more so."

Diagnosis.—Since chronic alcoholism manifests itself chiefly by nervous and digestive disorders, it may be simulated by the dyspepsia and accompanying nervousness which occur in failing health complicated by overwork or worry. A similar condition may be met with in women about the onset of the menopause, and in those who live on little more than strong tea.

The early stage of general paralysis of the insane and some cases of chronic alcoholism (pseudo-general paralysis) may closely resemble each other; in both there is a progressive degeneration of the higher centres, an impairment of inhibition, and a loss of self-control leading to disordered action. If definite exaltation of ideas be present or the irresolute lip movements be persistent, the diagnosis is usually clear; but there are cases of general paralysis in which the bodily symptoms are present without any mental alteration. In such cases signs of gastric disturbance, loss of appetite, morning sickness, and the absence of changes in the pupils would point to chronic alcoholism. Alcoholism may, however, play a part, though not of the first importance, in the production of the general paralysis of the insane. Since drinking may be a symptom of the early stage of general paralysis, the two morbid states may be concurrent. Careful inquiry into the history and symptoms will be necessary to decide in such doubtful cases (*vide* vol. vii. p. 721).

The tremors of paralysis agitans and of disseminated sclerosis can be distinguished by their special characteristics from that of alcoholism. The tremor of nervousness, hysteria, and senility may be mistaken for that of alcoholism; but further examination into the case will settle the diagnosis. Chronic alcoholism and tabes have several points of resemblance; the ataxic form of peripheral neuritis, as its name pseudotabes implies, may be confounded with locomotor ataxia. Gastric crises can usually be distinguished with ease from the gastritis and sickness of drinkers. The eye symptoms of tabes should always be looked for in considering the diagnosis of these two diseases. In malarial cachexia the nervous manifestations may closely resemble those of chronic alcoholism.

The treatment consists in cutting the patient off from alcohol completely; but unfortunately the existence of the drink-habit and craving render it very difficult to secure this in the conditions of ordinary life. Even if the patient do his best, he is usually unable to withstand the besetting habit. Strong moral suasion and a full knowledge of the effects of the evil may perhaps keep him an abstainer for a time; but where temptation meets him at every other turn, as in everyday life it must almost necessarily do, it is almost too much to expect him to remain so. In some instances residence in a house or nursing-home under the immediate supervision of a doctor is successful. A long sea voyage on a ship or yacht from which all alcoholic drinks are excluded is sometimes recommended, but the difficulties of preventing surreptitious alcoholic indulgence are considerable, and the opportunities for suicide are so numerous that this plan of treatment is seldom advisable.

Undoubtedly the best plan of treatment is for the patient to go into a sanatorium specially devoted to the medical treatment of inebriety, or into a Retreat established and licensed under the Inebriates Acts (1879-1900). At present a patient cannot be received into a licensed Retreat against his will, however extreme his drunken habits may be. To avoid any confusion, it may be pointed out that the Inebriate Reformatory Act of 1898 provided for the committal to reformatories of

"criminal inebriates" and "police court recidivists." Having voluntarily entered a Retreat under the Act, the patient remains there for a definite term, and if he escapes during that period he can be brought back. Temptation is thus avoided in a way which is almost impossible elsewhere, and at the same time the inmate is under skilled medical treatment. The term of detention in the Retreat should never be less than six months; a year is necessary in ordinary cases, but in severe or inveterate cases a term of two years is desirable. The form of request for admission to be signed by the patient, and the statutory declaration, to be made by two friends of the applicant, are appended.

Request for Reception into Retreat

Under the Inebriates Acts, 1879 *to* 1900

To the Licensee of the Retreat

I, the undersigned, hereby request you to receive me as a patient in your Retreat at , in accordance with the above-mentioned Acts, and I undertake to remain therein for
at least, unless sooner duly discharged, and to conform to the regulations, for the time being, in force in the Retreat.

Applicant's Signature

The aboved named ....signed this application in my presence, and at the time of his (or her) so doing satisfied myself that he (or she) was a person to whom the Inebriates Act, 1879, applies, and I stated to him (or her) the effect of this application, and of his (or her) reception into the Retreat, and he (or she) appeared perfectly to understand the same.

Dated this day of

Justice of the Peace for the County {
or Borough of } ....

Applicant's name in full

Address..

Description ....

Statutory Declaration in view of Admission

The Inebriates Acts, 1879 *to* 1900

We,
severally, solemnly, and sincerely declare that
who is an applicant for admission into the
is an Inebriate within the meaning of the Inebriates Act, 1879,[1] and we

[1] An "Habitual Drunkard" (or Inebriate) is defined in the Act of 1879 as meaning a person who is by reason of habitual intemperate drinking of intoxicating liquor, *at times* dangerous to himself or herself or to others, or incapable of managing himself or herself, and his or her affairs. The Secretary of State is advised that "intoxicating liquor" may include liquors other than alcohol, if their habitual intemperate use brings the consumer into the condition of an "Habitual Drunkard."

severally make this solemn declaration, conscientiously believing the same to be true, and by virtue of the Statutory Declaration Act, 1835.

Taken and declared severally at
in the County of
this day of 19 .
Before me
(*a*) *J.P. for the County or Borough of*
(*b*) *A Commissioner of Oaths*

To be signed by two friends of the patient before a Magistrate or a Commissioner.

The first step is complete withdrawal of all alcoholic drink. This naturally has a marked effect on the patient, who at once feels the need of his accustomed stimulant. Depression, restlessness, and some degree of collapse may result; but experience shews that no harm follows from the sudden and complete removal of all stimulants. There is no proof of the old belief that delirium tremens can be thus precipitated. The patient should be carefully but unobstrusively watched after his arrival, and his strength sustained by simple food, peptonised if necessary, beginning with milk, Benger's food, sanatogen (Mann), and then advancing to solid food, fish, and so forth. Feeding may be difficult from want of appetite, or from vomiting. Vomiting is far from being altogether an evil, as it removes tenacious mucus from the stomach, and so improves the conditions of digestion. The sickness should be treated by small quantities of liquid food, lime or soda water, alkalis, bismuth or effervescing mixture, or by 5-minim doses of ipecacuanha wine. Sleeplessness should only be treated by sedatives if it be urgent. Morphine, chloral, and cocaine should be avoided, lest the germs of a new craving be sown in the patient. Chloralamide, paraldehyde, trional, and bromides may be used if necessary; and the hypodermic injection of $\frac{1}{100}$ grain of hyoscine has been recommended. But before narcotics are employed, sleeplessness should first be combated by out-door exercise or fresh air, wet packs, or massage.

The bowels must be carefully attended to, and the appetite and digestion stimulated. Pepsin, bitters, tonics, and dilute acids are also of use. Much will depend on the way food is taken; as he improves the patient should get out a great deal, and should be well provided with suitable occupation.

Many drugs have been and are still used with a view of counteracting the craving for drink. Strychnine is often employed. It has been extensively given hypodermically, and has been combined with atropine. The latter drug has been strongly recommended. Nauseating drugs, such as ipecacuanha, apomorphine, have been added to the alcoholic beverages so as to generate a distaste. Tincture of capsicum in 5 to 10 minim doses has some effect in lessening the taste for stimulants. It is well, however, to remember that it is an alcoholic drink, and that it has been used as an intoxicant. Quinine, red cinchona bark, gentian, aqua

chlori, strophanthus, citrate of caffeine, coca, ergotin hypodermically, and other drugs have also been recommended for this purpose.

The so-called "gold cure" is said to consist in (1) hypodermic injections of strychnine sulphate $\frac{1}{100}$ gr., combined with atropine sulphate $\frac{1}{500}$ gr., or daturine sulphate $\frac{1}{200}$ gr., given four times a day: (2) medicine by the mouth every two hours during the day and evening, composed of chloride of gold and sodium, $\frac{1}{20}$ gr.; ammonium chloride, 1 gr.; aloin, $\frac{1}{25}$ gr.; fluid extract of viburnum, ♏x.; and tincture of cinchona, ♏xl.: (3) hydrotherapy, wet packs, vapour baths, and so forth. Dr. Fenn, from whose paper these details are taken, concludes that 60 per cent of patients after a month's treatment remain total abstainers. This method of treatment deserves unprejudiced trial at the hands of the profession, for the manner in which it has been exploited as a proprietary cure has naturally made orthodox practitioners look askance at it.

Numerous "specifics" and patent "cures" have been vaunted; some of them appear to contain strychnine and atropine. An analysis of fifty different proprietary medicines, some of which have been recommended as "temperance drinks," shewed that each contained alcohol in amounts varying from 6 to 47·5 per cent (27). It is not perhaps surprising that the condition of the patients is sometimes much worse after they have undergone these "cures."

Hypnotism has been employed with some success in creating a distaste for alcohol; while the patient is in one of the stages of the hypnotic state he is told that in future he will not be able to take alcohol: this is treatment by post-hypnotic suggestion. It should only be practised by a medical man, and in trustworthy hands is worth a trial. Its action is somewhat uncertain, but some admirable results have been published, and no doubt suggestion plays an important part in all "cures."

An anti-alcoholic serum, obtained from horses treated with large quantities of alcohol by the mouth, has been advocated by Sapelier for persons who constantly take alcohol but have no organic lesions such as arteriosclerosis, cirrhosis, tuberculosis, syphilis. Our knowledge of its use is not sufficient to justify a definite opinion as to its power or value.

Delirium Tremens

(Syn.—Alcoholic delirium, "The Horrors")

Delirium tremens seems to have been first recognised as a symptom-group, and separated from acute mania, by Sutton of Greenwich in 1813; and to have been accurately described by Ware of Boston, U.S.A., in 1831.

Etiology.—Though often described as acute alcoholism, and as sometimes coming on after a single bout of hard drinking, delirium tremens is usually an exacerbation in the course of chronic alcoholism, in constant soakers who are rarely drunk but hardly ever sober.

An hereditary taint, whether of insanity, alcoholism, or other neurosis, increases the liability to delirium tremens. This is probably the determining factor in many cases in which the symptoms have arisen acutely after a single debauch in a person not an habitual drunkard. The unstable condition of brain matter which is acquired by long-continued alcoholic excess in other cases is hereditary in the neuropath, and in the offspring of drunkards.

It was formerly supposed that delirium tremens was often caused by the interruption of the drinker's accustomed alcoholic stimulus. But the truth is that the distaste for drink is the beginning, and one of the earliest symptoms of an impending attack of delirium tremens—the result and not the cause of the disease. The attack, indeed, is often brought on by a bout of harder drinking than usual.

A severe injury, a sudden shock, mental or bodily, or the onset of acute disease, especially pneumonia, may in a constant drinker bring on the symptoms of delirium. After operations this form of delirium may occur; but it is practically unknown in childbirth, though it occasionally follows uterine operations. This state has been called "associated delirium" (Gowers), or "traumatic delirium" (S. West), and is dependent on two factors, (*a*) the long-continued toxic effects of alcohol, and (*b*) the depressing effect of injury or disease; so that, other things being equal, the prognosis is not so good in this form of delirium as in delirium tremens. Indeed, in ordinary cases of the disease there is often some minor exciting cause which acts as a "last straw" in the case of a soaker on the verge of delirium tremens; thus, there are transitional stages between the classical form of delirium tremens and that which appears to be precipitated by momentary accident. It has been thought that the exciting cause of delirium tremens is some secondary acute toxæmia, probably bacterial and from the intestinal tract (Ford Robertson).

Morbid Anatomy.—In fatal cases of delirium tremens the general lesions of chronic alcoholism may be found after death, as the delirium is so frequently an exacerbation of that disease.

The kidneys are usually large, and present the hypertrophy due to an increased functional activity. The liver is fatty and often much increased in weight from this cause.

Inasmuch as death is usually due to cardiac failure the heart is flabby, somewhat dilated, and often shews some fatty change in the myocardium (tabby-cat striation). From the manner of death hypostatic congestion of the lungs is commonly to be expected.

For other morbid changes the reader is referred to pp. 914, 916.

Symptoms.—In the premonitory stage, which is of variable duration, there is increasing restlessness and nervousness. Appetite for food is lost, and often even the taste for alcohol fails, or is turned to loathing; on the other hand, drinking may be continued right up to the full onset of severe symptoms. The night brings no real rest or refreshment, and passing slumbers are disturbed or broken by unpleasant or terrific dreams.

Hallucinations crowd into the waking moments, and begin to be troublesome also in the daytime; but at first they may be diverted or even dismissed by an effort of will.

The onset of the actual delirium in the second stage is indicated by an exaggeration of these symptoms. Tremor is a marked feature, and, though it is more manifest in the hands, tongue, and lips, it is only necessary to lay a hand on the patient's shoulder in order to detect vibrations all over him. This tremor is a further development of that of chronic alcoholism, and is part of a great and indeed universal muscular unrest which shews itself in continued though ineffectual activity. The tendons of the patient's fingers and the hands are continually at work, repeating the habitual manipulations of his trade or occupation, ceaselessly pulling up and picking at the bed-clothes, or scratching the body; he fidgets perpetually, and never rests. At times the sufferer wriggles under the clothes like an imprisoned animal. The mind is active enough, and is engaged in making plans for the future; or is swept into the whirl of hallucinations which can no longer be dismissed. The delirium is busy with a continual succession of ever-changing ideas, but each train of thought lasts for a short time only. A general uneasiness and a desire to move on possess the patient; he would pack up, start on a journey, or, as Trousseau expresses it, get away from himself. The activity of his mental processes is incontinently expressed by garrulous and incoherent talk, concerned chiefly with the figments of his brain; though surrounding circumstances come in for some contemptuous or querulous comments. Yet for a time, even in the midst of his multitudinous and imaginary pursuits, he can collect himself sufficiently to answer simple questions appositely. The face is anxious, the skin bathed in perspiration, the eyes furtive and perpetually moving, and the pupils usually dilated. The excitement is due to fear, engendered by delusions and by the visual and aural hallucinations. These are nearly always loathsome or terrifying—such as beetles, swarms of rats, fishes in the bed, horses' heads thrust through the walls, or yet more formidable creations of a morbid imagination. Later he ceases to recognise those around him, he sees in his friends or attendants designing enemies or derisive fiends, and fancies that insults and offensive remarks emanate from them, or that they are attempting to poison him or to feed him with offensive food.

The prevailing note of the delirium is one of terror: in order to escape, the patient is ever anxious to be up and off, and, if at liberty, would make an immediate exit without ceremony or dressing; sometimes indeed by the bedroom window instead of the door. He is suspicious, ever on the watch for some horrible object concealed behind the curtains of the bed or lurking in a corner of the room. Occasionally, under some hallucination or delusion, he may attack the attendants; but generally he can be controlled or humoured with tact. The pulse is now rapid and soft, the tongue moist, tremulous, and covered with creamy fur. The temperature is usually raised, in mild cases to 100° or 101°, and in severe cases to 103° F., with no local lesion to account for it; though

the apprehension of a latent pneumonia must never escape the mind of the physician. There is complete insomnia and absence of appetite.

The uncomplicated disease, as Ware pointed out, is self-limiting; and after two and a half, three, or four days, the acute stage, in most cases, undergoes a spontaneous amelioration. The patient, who has suffered from absolute insomnia, sinks into a quiet, refreshing sleep, and when he awakes is free from the delirium and hallucinations; though he does not lose the tremor for some time. In favourable cases convalescence is rapid. In severe cases, especially where there have been several previous attacks, the temperature may rise and fatal hyperpyrexia result; or again, pneumonia may set in; or the delirium may continue, and the patient pass into a low typhoid state; or collapse or death from syncope may suddenly close the scene. In other cases, again, the delirium may continue and signs of general failure supervene. Sometimes epileptic seizures come on, which are of very grave import.

Diagnosis.—Acute mania is the disease most likely to be confounded with delirium tremens; but the history, the tremor, the special character of the hallucinations, and the behaviour of the patient, will distinguish the latter from the former. To general paralysis of the insane with tremor there is some resemblance; but the mental exaltation of the excited stages of general paralysis should distinguish these patients at once from the terrified subjects of delirium tremens.

The question of diagnosis between meningitis and other forms of organic brain disease and delirium tremens does not often arise, though it appears to have arisen in former times; the presence of paralysis, severe headache, optic neuritis, irregular pulse, and oppression of consciousness point to organic brain lesion; while the presence of the characteristic delirium and tremor would at once suggest delirium tremens.

In fevers, such as enteric, where delirium may form part of the disease quite apart from alcoholism, it may at a given moment be difficult to decide whether the delirium be symptomatic—that is, due to the specific fever, or whether it be the form of delirium tremens ("associated delirium") which supervenes when injury or acute disease befalls a drunkard. The important condition, however, in this case is not the delirium, but the primary disease.

For the diagnosis between delirium tremens due to alcohol and the similar delirium due to withdrawal of morphine from the morphinist, the reader is referred to the article on Morphinism in this volume, p. 955.

Prognosis.—In first and uncomplicated attacks recovery is very general, though in a chronic alcoholic recurrence is extremely probable. Old age, previous attacks, and the presence of complications or other morbid conditions, render the disease a formidable one.

In "associated delirium" the nervous system is suffering on the one hand from shock due to the injury or disease, and on the other from the long-continued effects of alcohol; the prognosis is therefore worse than in ordinary cases of delirium tremens. Much, of course, depends on the

character of the injury or acute disease; in pneumonia a drinker's chance of recovery is poor, and double pneumonia is practically always fatal.

The state of the heart is of primary importance. A heart already dilated is a very serious condition. Signs of approaching cardiac failure —such as faintness, a small, irregular, very frequent (over 130) or running pulse, a soft, feeble, or inaudible first sound, or a murmur at the apex with an accentuated pulmonary second sound are of very bad omen. Pre-existing kidney disease is a grave condition, as uræmia may supervene.

If pneumonia appear in the course of the disease the outlook becomes very anxious. A temperature of about 103° F., especially in old and debilitated subjects, is always a cause of grave anxiety; it may be due to the insidious establishment of pneumonia, which may easily escape detection unless looked for from day to day, or it may be merely an index of the profound functional disturbance. Hyperpyrexia is usually fatal. Convulsions in the early stage, according to Sir W. Gowers, are not of much importance; but when they occur later the prognosis becomes very grave.

A patient who takes and digests his food usually does well; while cirrhosis of the liver or gastric catarrh, by interfering with digestion, diminishes the patient's chances of recovery. If the disease run on and sleep be not obtained, or obtained only in very insufficient amounts, there is great danger of exhaustion.

On amendment the symptoms may only partially abate and a condition of mental enfeeblement may persist. After repeated attacks some degree of weak-mindedness is often permanent.

There are then three degrees of the disease:—(i.) Uncomplicated attacks, in which the prognosis is good; (ii.) "associated delirium," in which the prognosis depends largely on the severity of the affection exciting the delirium; and (iii.) cases complicated by old age, debility, previous attacks, or the presence of visceral disease, in all of which the prognosis is very bad.

Treatment.—The most important points are food, sleep, management, and restraint.

Feeding is of great importance, seeing that the patient is in a half-starved condition, and, as a rule, has taken little food for a considerable time before the onset of acute symptoms. Careful feeding from the outset is very important, both for immediate relief and to prevent exhaustion and cardiac failure in the later stages of the disease.

Anorexia and unwillingness to take food (which may be due to a delusion that it is poisonous, disgusting, or offensive) require considerable tact and good-nature on the part of the attendants. If necessary, a nasal tube should be passed and fluid food thus introduced into the stomach at intervals of not more than three hours.

Beef-tea, peptonised milk, soups or broths, and, if acceptable, pounded fish or mincemeat should be given. Care should be taken, however, not to overload a stomach the digestive powers of which are almost certainly

much impaired by chronic catarrh. Vomiting must be combated by ice, effervescing draughts, lime-water, and careful feeding with small quantities; if it persist, nutrient enemas or suppositories may be employed. In the presence of severe complications, such as cardiac failure, pneumonia, or great exhaustion, cardiac and vasomotor stimulants such as digitalis, adrenalin, ether, and ammonia should be given by the mouth; but absorption is slow, and if the symptoms continue, hypodermic injections of digitalin, adrenalin, liquor strychninæ ♏ij.-v., or ether are indicated. A brisk purge should be given at the beginning of the attack, and repeated if the tongue be foul or constipation be present

In pneumonia inhalation of oxygen may be necessary.

Sleep.—The disease, as was shewn by Ware, tends to run a definite course. In favourable cases the acute stage terminates in sleep, after which the patient is no longer delirious. Probably as a result of this sequence of events, the belief arose that to cure delirium tremens the proper treatment is to send the patient to sleep. Sir T. Watson expressed this view of the treatment in his Lectures on Physic with no uncertain voice. For this purpose morphine or opium was largely given; in many cases the drugs failed to produce any effect for a considerable time, probably owing to delay in the absorption from the stomach. In this case large doses of opium were sometimes repeated, and with the result that the sleep-at-any-price treatment tended rather to substitute narcotic for alcoholic poisoning than to cure the patient. Instances of fatal results directly due to the "narcotic treatment" were not by any means unknown. On the other hand, the "natural" method of treatment aimed at giving no narcotics in ordinary cases, and letting the disease run its course. In prolonged sleeplessness, however, moderate doses of opium were given. Care is necessary, not only in deciding when measures to ensure sleep should be taken, but also in deciding on the means to be employed for this end.

Hypodermic injection is a very much more certain method of administering narcotics than by the mouth; hence morphine is more convenient than opium. After an injection has been given, the effect on the pupils should be watched and a second injection should not be given until the effect of the first has begun to wear off; so as to avoid any possibility of narcotic poisoning. Hyoscine hydrobromide $\frac{1}{100}$ gr. hypodermically sometimes acts satisfactorily, but is not very trustworthy.

It has been suggested that a pint of bitter beer or porter may be the best hypnotic in delirium tremens; this may be the case; but, as the use of alcohol tends to keep up the drink craving, its use must be carefully restricted.

Hot and cold packs have been highly recommended as a means of inducing sleep. Sir W. Broadbent advocates cold affusion; the patient lies on a blanket with a macintosh underneath, and is repeatedly sponged all over with ice-cold water, the skin being rubbed and dried between the spongings. Neither pneumonia nor albuminuria are contra-indications.

The best course is not to give hypnotics unless the case be prolonged,

or it appear that the patient is wearing out his strength and is in danger of exhaustion. Then, unless there be any marked contra-indication, such as severe lung or kidney mischief, morphine should be given hypodermically. If morphine be undesirable, a trial should be made of sulphonal, paraldehyde, chloralamide, bromides, trional, or veronal; combined, if need be, with a cold or hot pack. It must be admitted, however, that these drugs are very disappointing in this disease.

Restraint and General Management. — Constant watching is of great importance; in the acute stage the patient, if left alone for a moment, may jump out of the window, or commit suicide in a most determined manner. Two strong nurses should be in attendance, and should never quit the room for an instant until relieved.

The patient should be placed in a cool, quiet, and dark room, so as to favour the advent of sleep; and should lie on a low bed preferably padded—beds with sides of woven wire are now made, and are very useful—or on a mattress on the floor of a padded room. No mechanical restraint must be used unless the difficulties be exceptionally great. If two attendants be insufficient, the number must be increased. In the presence of a sufficient number of attendants accustomed to the management of such cases, mechanical restraint is not needed. All such patients are quick enough to see their moments for submission or for escape. If mechanical restraint be absolutely necessary, a strong sheet may be tucked well and tightly down on both sides, but no straps or folds across the body are permissible, as such bands arrest respiration, if they do not now and then break a rib. Strait-jackets are a survival of the dark ages, and leather wrist-bands and bandages abrade the skin and give rise to sores. An attendant who kneels upon a patient must be instantly dismissed. Very much can be done without any restraint by attendants who know how to humour the patient, and have tact in soothing and diverting him.

As convalescence advances attempts to overcome the drink habit should be made by moral suasion, and by the administration of strychnine, atropine, capsicum, and so forth. After recovery the patient may with advantage go into a licensed Retreat under the Inebriates Acts, in order if possible to be cured of the drink habit. (*Vide* p. 926.)

Acute Alcoholic Mania and Melancholia.—In persons with an hereditary nervous irritability alcoholic excess may be the immediate cause of an outburst of acute mania or melancholia.

Alcohol is thus, by accident as it were, the exciting cause of an attack of acute mental aberration; but the symptoms may not be in any way characteristic of alcoholism. This subject is therefore part of the section on insanity (*vide* Vol. VIII.), and will not be further treated here.

Dipsomania.—Dipsomania or oinomania is a form of recurrent mania or psychical epilepsy attended with impulsive drunkenness. It occurs periodically at intervals of two to twelve months in persons who at other times are perfectly sober and free from the drink craving. It attacks only those who have a decidedly hereditary taint, or who have acquired a

certain instability of the nervous system from head injuries, sun-stroke, and the like. In women the periodic outbreak often, but by no means always, coincides with the menstrual flow.

The premonitory symptoms are restlessness and irritability of body and mind, sleeplessness, and mental depression and change in conduct. After ineffectual struggles the barriers of self-control break down, often towards night or in the night; alcohol in some form is taken copiously, and the patient may then drink straight on, and be continuously drunk for a week or a fortnight; or he may impulsively drain a decanter of wine, and rise in the morning released from temptation.

When the outbreak has been a disgraceful one the sinner is overcome with grief and shame, and pursues the tenor of a sober and regular life until the next periodic attack causes him again to run amok in alcohol.

In dipsomania, between the recurrent attacks there is no drink craving and no great danger from temptation; it thus differs from chronic alcoholism. It is doubtful whether it can ever be cured, though the attacks may for a lifetime be so brief as to remain unknown to the world. In those cases in which one heavy draught suffices to allay the craving, there is often indeed no apparent intoxication, an immunity we may occasionally observe in persons who drink deeply during violent neuralgia: the dose seems to be expended on the restoration of equilibrium.

Dipsomania evidently belongs rather to insanity than to alcoholism (*vide* Vol. VIII. p. 269; and for Treatment by Hypnotism, p. 421).

H. D. Rolleston.

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OPIUM POISONING, AND OTHER INTOXICATIONS

By Prof. T. CLIFFORD ALLBUTT, M.D., F.R.S., and Prof. W. E. DIXON, M.D.

IT is often said that the craving for stimulant and narcotic drugs is a vice of civilisation; the labour of righteousness and wisdom is too great a burden even to be borne—far too great to be contemplated. The most complacent of men has moods in which he wishes he were again a child; in which he regrets the momentary joys, the carelessness of things to come: once again he would "play around the den of sorrow." The "instinct of self-preservation" is something more than a clinging to bare life; it contains a desire for the fulness of it, for uncalculated pleasures, for happiness which comes without scheming, for release from the scheming which does not bring happiness after all: a man will lay down his life without a murmur, but if it is to be lived he would live it well.

It needs no long consideration to tell us that these despondencies and these regrets are no fruit of civilisation: the yearning for a deep draught of life is of all time; savage and civilised man alike are ready, if occasion serve, to drown care in fantasy, and through some magic arch of ivory to escape into the land of the blest.

With the advance of "civilisation" the use of such gramarye as lies in herbs is not more but less prevalent. Noah, as soon as the ark was well off his mind, was at least as ready as a city broker to seek a careless joy in wine. To bring higher kinds of excitement and variety into the lives

of those who have laboured and striven, or lain in dulness and monotony, is the gift not of barbarism, but of the arts.

The iron rule of the tribal savage is compensated by times of corybantic excitement; and when a whole clan gets drunk at once there is no room for scandal; even when a whole village gets drunk there is no one, except a few wives who do not count, to condemn the festival: but if in the midst of a sober community we individually seek these fictitious consolations we find that scandal is awakened and moralists are alarmed. On the other hand, in times like our own no doubt the modes of indulgence are more refined and the occasions of it more secret. In the service a soldier given to drink is kept more or less straight by discipline and the lack of private opportunity; the same man on his discharge disgraces himself, the restraints upon him are less constant and severe. The more civilised, that is, the more various and interesting life becomes, the more, no doubt, will be the occasions of secret indulgence; but the temptation will be less, and, though we shall hear more of them, the sinners will be fewer.

Wherein lies the harm of "stimulants" and narcotics? If they are short cuts to happiness, why not use paths so pleasant? Do we not ourselves prescribe these things to men and women racked with pain, or worn out by labour and sorrow? That sometimes and for momentary purposes, or to those for whom all hope of life is void, we do administer them, is true; but we do it with the utmost precaution, knowing that they act by reducing life, not by enlarging it; and, moreover, that in their degrees they create an organic need which when satisfied brings no reward. Food to a hungry man fortifies his life; love to a lorn man enlarges it; sleep and joy refresh us for new adventures: but habitually to satisfy the craving for drugs like morphine and alcohol, brings nothing home but the continual dropping of their endless importunity. And this is because, in maiming life to diminish the capacity for pain, we likewise diminish the capacity for happiness also.

The highest functions, though they yield the most, fatigue us most: the machinery is at once the most complex, the most costly, and the least automatic. By the ardour of aspiration or the steadfastness of faith we strive to bring these functions into habits, and thus to build up pleasures to abide with us; yet in this exercise the frailty of man, civilised or barbarian, is revealed. Now it may not be true to say that opium and other such agents cannot do anything for the higher life; to some brilliant men the very treachery of them has lain in the fact that they have some mask of virtue. It is alleged of many such agents that their stage of oblivion is preceded by a stage of stimulation. How far this stage is but apparent, or how far it is real, is hard to say: a sedation of certain parts may throw other functions into an eminence which may be positive or may be relative. In persons of vivid sensations, to calm the commotion of conflicting impulses may be some enfranchisement even of the highest faculties. The stories of such lives as that of Coleridge suggest such a possibility; or even the effects of a quiet pipe upon smaller

persons. In customary use of a particular sedative the system ceases to resent its presence, and thus the initial stage of apparent stimulation, which seems, if delusively, to play a part in the action of all narcotics, is less alloyed; though on the other hand the doses must be increased, and a time arrives when the drug does little or no more than satiate the craving for its own repetition. Again, after the sense of excitement, on the way to the stage of depression, a middle moment of grateful peace and irresponsibility is experienced: "Is there any peace in ever climbing up the climbing wave? Let what is broken so remain. The gods are hard to reconcile." This blissful period, however, as nervous degradation becomes established, is encroached upon by misery, as is the pause of the heart in disease.

The only common factors which the vast group of paraffinoid hypnotics possess are a general power of diffusion into the uninjured cells of living tissues, comparative insolubility in water, and a greater solubility in fat and fat-like compounds. Hans Meyer and Overton, working independently, have constructed a hypothesis which assumes that in the living body these hypnotic substances dispose themselves on the one hand according to their relative solubility in fat-like compounds (lecithin, cholesterin) which are especially contained in nervous tissues, and water, which is represented by the blood, lymph, and other tissues, on the other. The narcotic action of a substance is therefore regarded by Meyer as a function of solubility in fat-like compounds. In support of this hypothesis it has been shewn by many examples that all inert chemical substances which can diffuse into living cells produce narcosis to a degree roughly proportional to their relative solubility in fat and water. The most powerful narcotic substances are those which combine a very slight solubility in water with a very high solubility in olive oil or more especially in brain-lipoid; the foreign substance by collecting in nervous structures impedes activity, and all the cells, motor as well as sensory, are affected in the same way. We have thus an intelligible hypothesis, the "partition coefficient theory," as it has been termed, to account for the action of a great group of chemically inert drugs, which, though acting in the same way, have no chemical properties in common. It is not, however, to this group of indifferent hypnotics that morphine belongs: its mode of action is completely different from theirs. Morphine exerts a specific depressant action upon sensory nerve-cells; and the motor nerve-cells, at all events after the moderate doses of the drug, are not influenced. So that the patient under morphine has fewer sensory impulses of all kinds, but the motor cortex is unaffected and in animals responds to electrical stimulation in the usual manner. But morphine has one action in common with the indifferent hypnotics: it produces a sequence of symptoms in man and animals which can be explained most readily on the assumption that it depresses the various cerebral centres in the reverse order of their development, beginning with the psychical centres and working downwards to the medulla, thus affording a good example of the order of dissolution.

The truth is, there can be little doubt, as Schmiedelberg first pointed out, that narcotics have no element of primary stimulation in them; that from the first they arrest the function of the parts to which they attach themselves, the parts first invaded being the highest planes of nervous function. Thus released from control the functions of the lower systems take their play; and necessitous man, no longer "amazed among the thorns and dangers of the world," is reduced to the light and careless livery of the child. Gradually, however, the drug, tightening its hold on the higher, penetrates to the lower planes of structure, and so perverts even the grosser viscera of the body that gaiety ends in abasement.

Poisoning by opium falls readily into the two chapters of Acute poisoning and Chronic poisoning; in the former case the drug may or not be wilfully taken, in the latter wilfully always. Opium is never used, except in the case of infants, as a means of slow murder, for which purpose it is unsuitable.

Acute Opium Poisoning.—The action of opium generally corresponds to the action of morphine but not always, for opium obtained from Persia and India (which is unsuitable for use in medicine) often contains a large amount of narcotine, sometimes even more than of morphine. Narcotine has a strychnine-like action on the cord, that is, it produces clonic convulsions. Morphine and narcotine are not, however, diametrically opposed in action; the characteristic feature of the former is depression of the sensory cells of the brain and comparatively little action on the cord, whilst the stimulant effect of the latter on the cord masks the cerebral effect. Hence certain varieties of opium have a more convulsant action than others, and this no doubt accounts for some of the so-called cases of idiosyncrasy.

Although opium or morphine is used so rarely by poisoners, it is far otherwise in respect of another criminal purpose, namely, of suicide. Persons seriously suicidal often seem indeed strangely indifferent to the amenities of the practice. So far from invoking a gentle angel of death, such persons, in their hatred of life, often seem to find a savage delight in rending the garment of the flesh violently from them. Moreover, temptation to suicide usually presents itself to the actor in a concrete form, as shooting, drowning, poisoning, and so forth: thus each suicidal person has his own fashion of seeking death. Still, among the less bloodthirsty suicides—in those who put an end to themselves, not in abhorrence of life, but in pique, fear of shame, or fantasy—opium, which offers a calm and painless death, is often the chosen means.

Again, opium is so commonly used as a medicine or as an indulgence, and, as a liniment or the like is so often at hand, that accidental poisoning by its means is no rare mishap. Recent legislation, however, or modern intelligence which is more effectual, has lessened the number of these accidents.

The varying susceptibility of various persons to opium is remarkable. The extreme sensitiveness of children to the drug is well known; and,

indeed, some adults fall into a syncope on taking very small quantities—such quantities, for example, as may be contained in ordinary cough syrups. Others again shew a remarkable tolerance of opium, and, as in them the preliminary "stage of stimulation" is prolonged, or is unblurred by malaise (as in the case of De Quincey and probably of Coleridge), they are the more liable to fall into habitual indulgence.

It is said that on ingestion of overwhelming doses of opium semblances of excitement are absent, or nearly so. This statement must be taken with discrimination. Cases are recorded by Tardieu and others, under the name of "*la forme foudroyante*," in which the patient falls almost at once into coma; the limbs are relaxed, and no response can be elicited from the skin or the conjunctiva. Death, in the coma which appeared at the outset, may occur within an hour, or even in half an hour. No delirium or convulsion is seen, and the final phenomenon, dilatation of the pupils, is seen almost or quite from the beginning. We shall make, of course, the obvious reflection that the characters of the symptoms may depend not merely on dose, or on personal idiosyncrasy, but on the conditions of absorption at the moment of ingestion.

In these fulminating cases symptoms of excitement may be imperceptible or altogether wanting; and this is more likely to be the case if a fatal dose of morphine be administered subcutaneously. But in ordinary circumstances, when the symptoms come on more gradually and may take half an hour or an hour to develop themselves, some signs of apparent excitement are not wanting. The skin is hot, the pulse is quick, the heart throbs or palpitates, the head may ache, or dreams merging into delirium may be witnessed for a passing interval. In this state, moreover, the pupils are minutely contracted. In some cases the agitation and hallucinations are terrific, and the reflexes vivid; such cases are more usual in women and children possessing a highly emotional temperament than in men, but they are commonest in Malays and some other Eastern races. Cats (Felidæ) are peculiar among animals in that morphine always induces great excitement in them; the animal rushes wildly about, apparently without an object, not always avoiding obstacles. This state does not depend on direct stimulation of the motor area, for electrical excitation of this part elicits a normal response. The excitement must be explained by a dissolution of the controlling centres. Why the cat should be affected in this way more than other animals, it is difficult to understand; but drugs which attack the central nervous system always exhibit these differences in different animals and not infrequently indeed in animals of the same genus. To exemplify this it is only necessary to refer to the varieties of alcoholic intoxication in man, the lacrimose, pugnacious, hilarious, and so forth; all of which are determined by the man's habitual moods, one variety being usually constant for each individual.

Stupor then gradually gains upon a period of excitement, which may be virtually absent, more or less transient, or more or less confined to certain regions or functional groups of the body. The face becomes more dusky, the blood-pressure falls a little, and the breathing is more

slow and stertorous ; no external stimulation can awaken a response ; the limbs are relaxed, the pulse feeble and irregular. The secretions, which, with the exception of the sweat, have been falling in quantity from the beginning, are now suppressed ; the sphincters are relaxed, and the pupils dilate. During the advance of this comatose state the patient is not only unconscious, but ere long he is not to be aroused by any noise or agitation ; though for a little while such means may bring a returning flush to the cheek or a little more force into the respiration. If death occur, it comes by failure of the respiration, which becomes uneven, tidal, and even so slow as 10 in the minute. We have once or twice seen slight convulsive movements during the coma, but in the earlier stages of it. Some writers speak of intercurrent moments of awakening ; at any rate false semblances of amendment are as common as they are deceitful.

The duration of the coma is rather variable, but never lasts more than a few hours ; the duration depends, indeed, less on the quantity taken than on the temporary conditions of absorption and the tolerance of the individual. A persistent improvement in the depths of the respirations and in the colour of the skin would be the first sign of recovery ; though, as we have said of false semblances of recovery, such signs must not be too readily accepted : moreover, relapses are not uncommon, due probably to some renewed dispersion of the poison into the system. The morphine is excreted into the stomach and intestines, and this may be reabsorbed and so work in a vicious circle. In acute cases in children Sir T. Stevenson says that "the second stage of intoxication is often wanting, and severe collapse and complete unconsciousness rapidly supervene."

Diagnosis.—Although the candidate for a medical degree is often invited to give the points of diagnosis between acute poisoning by opium or by alcohol, and of these again from hæmorrhage into the pons Varolii, yet in some cases a positive diagnosis is out of reach ; and in many more a diagnosis can be founded only upon such incidental circumstances as the smell of opium in the vomit or breath, or on such evidences of suicide as mental disorder, purchase of the drug, empty bottles, and so forth.

Unless the patient be in the final stage, the pupils will be equal and closely contracted, and the unconsciousness profound. An alcoholic patient is rarely intoxicated beyond the points of struggling and swearing, under which emotions his pupils often vary in size. Albuminuria may result from the prolonged use of opium : on the other hand, evidence of the presence of morphine in the system of a comatose person does not exclude uræmia ; it might even suggest it. From syncope the distinction should not be difficult, except in the last stage, when the state may partake of the syncopic character ; yet even then the stupor and abolition of reflexes may direct the observer aright. General convulsions at the outset, if the outset were witnessed, would not suggest opium, but rather uræmia, or hæmorrhage on the surface of the brain ; here again the almost invariable equality and pin-hole contraction of the morphinous pupils may assist us. A unilateral symptom, whether paretic, spasmodic, or ocular, would divert the attention from opium ; and

a rise of temperature would direct our surmises towards cerebral hæmorrhage. In diabetic coma we may have the smell of the breath to help us; and the examination of a specimen of the urine, which may be drawn off by the catheter, is important. Tidal breathing (Cheyne-Stokes) may occur in opium poisoning, chloral poisoning, cerebral hæmorrhage, diabetes, or uræmia; its significance is a deficiency of oxygen in the blood, and the condition can generally be removed by the inhalation of oxygen. The state of the pupils usually suffices to distinguish opium from chloral poisoning, and from this their minute and equal contraction with sweating skin must be distinctive.

Morbid Anatomy.—There is nothing in opium poisoning to distinguish the brain from other conditions in which cerebral "congestion occurs"; nor is there any constant morbid feature of the lungs or heart. Prof. Osler, however, reports that extreme passive congestion of the bases of the lungs takes place, as in cerebral apoplexy. Medico-legal considerations do not come within the limits of this work.

Treatment.—The first indication, it is needless to say, is to empty the stomach: even if it be known that the poison was taken hypodermically this operation must not be omitted, as morphine in smaller or larger quantities finds its way into the stomach from the blood. To empty the stomach, the siphon is the proper means. Emetics would probably act slowly or not at all: in the use of potent emetics there is a risk of smothering the spark of life. Yet if no siphon be at hand, an emetic of mustard and water must be administered; or apomorphine may be given under the skin, but it is a very depressing agent, and in so profound an apathy the reaction to a drug, even subcutaneously introduced, may be slow and imperfect; perhaps it may be safely given with strychnine. Besides emptying the stomach at half-hourly intervals, to remove the successive infiltrations of the poison which are excreted into its cavity, can we do anything more?

It is the custom, a custom in which we have loyally taken our part during many a weary hour, to "arouse" the patient by bullying him. He is cuffed, dragged up and down the room by relays of enthusiasts, pinched, singed, flipped with wet towels, bawled at, and racked by electric currents strong enough to drive an omnibus. Now, although these measures may, no doubt, animate a medical student with his first real sense of doing some good in the world, yet they are almost as useless as barbarous. What possible end can be served by flagellating a senseless corpse? So long as the poison oppresses the nervous centres it is useless; when the poison is clearing away it is otiose. Two good purposes may possibly be credited to them: it may be alleged that such efforts raise arterial blood-pressure, and that the wet-towel business may stimulate the respiratory centre. Now we know little enough about the conditions which modify blood-pressure; that muscular exercise, or at any rate the first initiation of it, raises the pressure is true; but to this end there must be a function on the part of the patient: to haul a dummy about the room will only raise the blood-pressure of

the attendants. If the respiratory function may be stimulated by "towel-ending," far be it from us to deprive the patient of such attentions. But seeing that we are in some measure independent of this drowsy nerve-centre, and can for a while perform the patient's respiration much better than he can, why resort to dubious means? Instead of all this rough-and-ready turbulence, relays of attendants should be deliberately organised for artificial respiration, and the respiration thus kept going in order that, as the poison is excreted, if happily it may be, the awakening centre may find that its work has been going on during its abeyance, and that its machinery is in working order. After clearing the stomach, artificial respiration, the inhalation of oxygen, and the application of warmth to the body and limbs, are the first and chief means of restoration. A lowered temperature is one of the constant effects of narcotic poisoning, and is apparently due both to depression of the heat-centre in the corpus striatum and absence of voluntary movement. And one of the most important means of preventing death from collapse is to ensure continuous application of artificial warmth to the patient's body. Now, can we do anything else? Are there any specifics which have the power of neutralising or counteracting the opium or the morphine? Prof. Binz and Sir Lauder Brunton say that atropine has an antagonistic action to opium up to a certain point, chiefly in its action on respiration—atropine acting as a stimulant, and morphine as a depressant on the respiratory centre. We have administered atropine in several cases of opium poisoning, and have thought with occasional advantage, but certainly not with any great or consistent success. These drugs, though antagonistic as regards their effect on the medulla, probably do not act on the same cells. Morphine depresses the sensory nerve-cells, and its effects are due to a deficiency of afferent impulses. Atropine, on the contrary, appears to act on the efferent impulses, probably the motor nerve-cells are rendered hyper-excitable. In view of the depression of the respiratory centre it is well to inject small and cautiously repeated doses, watching the effects upon the function; but blindly to pour in a second virulent poison upon the first can never be pardonable so long as our knowledge on the subject remains as scanty as unfortunately it is at present. The obvious antagonism of the actions of these drugs upon the pupil has caused too much confidence in the completeness of their opposition: the antagonism is only apparent, for the morphine produces its effect centrally, whilst the atropine acts by depressing the terminals of the third nerve in the iris. Pure caffeine, however (not the citrate, which is not so constant a drug), may be safely injected subcutaneously in doses of five grains; the dose may be repeated, and injections of hot infusion of coffee or green tea may be thrown into the rectum. So far, then, our means seem to be evacuation of the stomach, injections of pure caffeine and hot coffee, a cautious trial of $\frac{1}{50}$ to $\frac{1}{30}$ gr. of atropine, and artificial respiration, with perhaps the inhalation of oxygen, as the function becomes more shallow or uneven. The caffeine is an excellent

medullary stimulant, and it is better to rely on this aid than to give alcohol so freely as is often recommended. It must be remembered that alcohol, although possibly of use as a cardiac stimulant, is a narcotic poison, stupefying the brain. Morphine, even in the largest doses, has no direct action upon the heart; if the heart shews signs of failure it is due to other indirect causes, such as inefficient respiration or collapse, following an excessive fall of temperature.

Of late years potassium permanganate has been warmly recommended. It is, unfortunately, only destructive of that portion of the alkaloid present in the stomach, and then only if the stomach be nearly empty. By this contact the salt oxidises the alkaloid, and thus reduces it to a harmless state; and it must be admitted that Dr. Moor has shewn by his observations, including a number of experiments on man (such as the administration of three to five grains of morphine followed by the permanganate), that the remedy has considerable power upon the poison while the latter is still in the stomach. It is clearly our duty, then, to inject a solution of the potassium salt (ten grains dissolved in six ounces of water) into the stomach at the time of using the stomach-tube; or, if this cannot be introduced, to administer it by the nasal tube. Although the introduction of the permanganate into the stomach cannot directly neutralise morphine already absorbed, yet we have seen that small quantities of morphine return to the cavity of the stomach, even when the drug is inserted subcutaneously (Kandidoff). So far as this be true, the introduction of the permanganate is always a reasonable measure; and Dr. Moor relates a case in which morphine was found in the stomach thirteen hours after 150 grains of opium had been swallowed. He directs us to administer half a gramme to a gramme of the antidote in an ounce of water every half-hour by the mouth; or as frequently to wash out the stomach with a weak solution of the permanganate. It is hardly necessary to point out that the hypodermic injection of permanganate is quite useless, as the drug is reduced before it reaches the circulation.

CHRONIC POISONING.—**In Children.**—Of the slow poisoning of infants and very young children by those narcotics which contain opium we have little or no experience. We are told that such practices may be suspected when an infant dwindles, turns sallow, and is constipated, or has diarrhœa with offensive stools. Incontinence of urine, if continence had been reached, may recur. With its sickly looks the patient loses appetite, and, when not under the influence of the sedative, is irritable and sleepless; hence of course the excuse for continuing the use of the drug. In children, as in adults, pruritus and albuminuria may be observed. It is said that not only are elixirs, and the like, containing laudanum or other opiates given by the mouth to children, but even clysters also. The difficulty of treating such cases lies in the discovery of the cause of the ailment; on such discovery gradual withdrawal of the drug is all that is required. Mattison cites a case of chronic opium poisoning in childhood. A baby of seven months, when first seen, presented the shrivelled and

wrinkled appearance of an old man. The child had been normal at birth, and had thriven up to the age of four months, when, in order to quiet it when fretful, paregoric was given to it. Laudanum soon became necessary, and in increasing doses, so that when the child was first seen by the physician it weighed only seven pounds, and was very weak and emaciated: it was taking at this time no less than an ounce of laudanum daily. The laudanum was reduced by one drop at each dose, and at the end of a month the child had become plump and well again. It must not be asserted, on the other hand, that opium ought never to be administered to infants: we have the authority of Dr. Eustace Smith and others for saying that opium may be of "extreme value" in their ailments. Dr. Eustace Smith tells us that no ill effects will ensue if care be taken to begin with a sufficiently small dose, and to postpone a second dose until the effects of the first have been ascertained. Thus, for a child of one year old suffering from purging, if one minim of laudanum have not produced drowsiness, another may be given in six hours; with these precautions the remedy will be well borne three times a day (cf. Vol. I. p. 257).

A curious assertion has been made by Dr. Happel, that the children of morphinists often shew at birth the "symptoms of withdrawal" of the drug; that they readily become cyanotic, and need morphine and alcohol to rear them. Dr. Crothers, in the same discussion (42), added that these children not rarely become themselves morphinists or alcoholists in after-life. It must be difficult to distinguish between such a direct and specific influence and the more general forms of neurotic inheritance. Four cases recur to our memory: in one case the child of a morphinist father was marked only by asthma, which probably was part of a neurotic inheritance independently of the morphinism; and the children of three morphinist mothers were fairly healthy. As the use of morphine diminishes sexual desire, the children of morphinist mothers are more commonly met with than of morphinist fathers. Such children are no doubt born in poison, and need most careful feeding and management to attain a fairly healthy state (Gossmann). Erlenmeyer saw a healthy child born of two inveterate morphinists; but on the other hand he reports that many such children are sickly, frail, and bloodless.

Chronic Poisoning in Adults.—(SYNONYMS: *Morphinism*, *morphiomania*, *Morphiumsucht.*)—We now enter upon the most important chapter of our subject, namely, of the opium-eater or morphinist. Chronic opium habits may be divided into three practices—that of the opium-eater, by whom the drug is swallowed in the crude state or in preparations of the crude drug, such, for example, as laudanum; the opium-smoker, who inhales sublimated products of it; and the morphinist, who injects a solution of morphine under the skin, or in some cases into a vein.

It is neither possible nor necessary to enter into the whole matter of the use and abuse of opium by the *opium-eater*. The reader who has perused any great part of the evidence taken by the Opium Commission in India is aware that opium is used by a vast number of His Majesty's subjects, and by thousands of others beyond his dominions, in the faith

that the drug is useful to them, and is not abused in any ordinary sense of the term. Whether it be taken as an antidote to fever or other ill-health, or as one of those nervine agents which all people, civilised or uncivilised, discover—as we have discovered tea, coffee, and tobacco—to soothe the nervous system, to restore it after fatigue, or to endow it with powers of extraordinary endurance in lieu of rest or food, opium is used, rightly or wrongly, in many Oriental countries not as an idle or vicious indulgence, but as a reasonable aid in the work of life.

A patient of one of us took a grain of opium in a pill every morning and every evening of the last fifteen years of a long, laborious, and distinguished career. A man of great force of character, concerned in affairs of weight and of national importance, and of stainless character, he persisted in this habit, as being one which gave him no conscious gratification or diversion, but which toned and strengthened him for his deliberations and engagements. He did not use tobacco, and the opium seemed to stand to him in the place of that aid. The habit had arisen on the not improper advice of a physician, who had found him liable to intermittent "gouty" glycosuria. The opium was continued, however, not on this account, but for its own sake. This case is the only important one in which we have had occasion continuously to observe a moderate use of the drug in this country. In temperate non-malarious climates opium is not required, or is better displaced by tea or tobacco. Opium is still largely used by dwellers on the levels of England which at one time were malarious; either because there is still in such districts some remnant of maleficence, or, more probably, from old custom. It may, however, be taken as a safe rule, in our own country at any rate, that the familiar use of opium in any form is to play with fire, and probably to catch fire. Of the moderate use of opium in other countries no final opinion can now be given; in adults of good character the physician must use his own discretion, but he must ascertain that the habitual daily allowance is not an increasing one. Any temptation to such an increase—say beyond two grains a day—should determine the habit at once. One who has given himself up to the use of opium may not uncommonly consume as much as half a pint of laudanum in twenty-four hours; and it is asserted that an Oriental may consume "several grammes" of opium in a day. Among Mohammedans opium is strangely supposed to have aphrodisiac virtues; they also use it as a surrogate for the forbidden alcohol, and, with more excuse, to help them over those terribly protracted fasts of which we in the West have no experience.

An important question which has lately received considerable attention is that of tolerance. Two views of this phenomenon have been held: the one, that it depends on the gradual habituation of the tissues to morphine; the other, that this substance undergoes some change in the body; and as one of its products of oxidation, oxydimorphine, possesses scarcely any action it was natural to suppose that the production of this substance in the body would explain the condition. At best this is a surmise, and proof is wanting. Morphine, unlike most alkaloids, is

excreted into the alimentary canal, and much of it can be recovered from the fæces. Faust has shewn that after the hypodermic injection of moderate doses into dogs 66 per cent can be extracted from the fæces. By gradually increasing the dose this amount diminishes, until after a time no morphine is excreted either in the fæces or urine; moreover, after the death of the animal none can be extracted from any of the organs. Yet in these animals the ordinary symptoms of morphine were produced by enlarging the dose. Faust, in our opinion, legitimately concludes that habituation to morphine is due to increased capacity of the tissues to destroy it. He employed sodium oxalate, a drug which is excreted in the urine, as a control experiment, and found that when the dose was increased the drug was excreted by the kidneys in the same relative amount. This tolerance to morphine is not due to an antitoxin, for no specific substance of this nature can be obtained: it seems rather to depend on the oxidising power of protoplasm. Since bio-chemistry has shewn us how large a number of the specific chemical reactions physiologically occurring in the body are brought about by ferments, we may presume that the oxidation of morphine is effected in the same way.

Opium-smoking, whether in Europe or elsewhere in the world, suffers condemnation not because of the direct mischief of it, which may or may not be great, but of the degrading circumstances of its pursuit; in Eastern towns it is the resource of the scum of the earth, and is associated with every kind of abomination. Apart from its brutish surroundings, the smoking, subtle and seductive as these fumes may seem to be, cannot in itself be so mischievous a practice as opium-eating or morphine injection. Throughout this article, for brevity's sake, we have assumed that the effects of opium and of morphine are virtually the same, as ordinarily they are; but the practice of opium-smoking seems to indicate some important differences. Morphine, if volatilised at all, is thus dissipated in very small quantity, and of the sublimate a great part must be collected about the pipe. None of the bitter taste of the alkaloid is perceived in the mouth of the smoker. The total amount of morphine in one charge is calculated to be no more than three milligrammes; now, even if twenty pipes are smoked in a day, which is a liberal allowance, we have only a possible total of six centigrammes (about one grain) of morphia burned in a day; the chief part of this is literally burned and not sublimated at all, and of the rest more or less is deposited about the pipe. A modern lady morphinist would put the remnant under her skin six times a day, and call upon us to admire her moderation. Again, the smoker does not prize those qualities of opium which contain the larger proportions of morphine, but prefers the Indian and Chinese drugs (principally that of Patna), which contain only 3 to 7 per cent of morphine. Nevertheless the evils of opium-smoking are too patent to be reasoned away; and arguments for its innocence are sufficiently confuted by the existence and results of the practice. There is, no doubt, some maleficent quality in opium-smoke which enslaves the smoker.

Opium-smoking obtained a certain vogue in the United States, until it was ousted by the syringe; on the other hand, curiously enough, large quantities of morphine are sent to China itself as a "cure" for opium-smoking. The morphine is made up in powders, each of which contains about a third of a grain in some rice-powder; the powders are taken at lengthening intervals until the habit is broken.

The opium-smoker is not rarely a man of active habits; and in moderation, like other uses of such drugs, the practice may enable the user to do a great deal of work on little food. Indeed the testimony of many travellers seems to assure us of this. In such persons it may do no more harm than the inhaling of cigarettes. The first effect of the drug on the Chinese smokers is to render them more loquacious and animated, and to give them an elated sense of superiority, effects to be attributed to depression of the higher or controlling centres in the brain. Gradually conversation drops, the devotee becomes drowsy and passes into a deep sleep, from which he awakes in from one to four hours. Just as alcohol brings out the character of a man, so it is with the opium-smoker; his behaviour in the first stage is determined by his character and habitual mode of thought. Thus the opium-pipe renders the Malay outrageous and quarrelsome.

In depraved persons and imbeciles, who will abandon themselves to anything, it gradually produces the opium cachexia—"the emaciation, leaden pallor, languor, and utter neglect of person and duties of life," in which the influence of morphine seems to manifest itself. In competition with the smoking-shops, there are now shops where injections are to be had at so much the syringeful.

Morphine injection is by far the most important agent in the story of the consumption of this drug. The opium-eater was a portent, almost a bogie; the morphinist, with her syringe and case of tablets, is a familiar object in our consulting-rooms, if not in any nearer relation. This terrible vice—a vice scarcely less than that of alcoholic drunkenness—is perhaps somewhat on the decline; partly because those who would draw to it are better aware of its evils, partly because medical men are better aware of the danger of putting the means of indulgence within the reach of a patient. On the first discovery of the method the effects of small injected doses were seen to be so beneficial, so prompt in relief, so free from the digestive derangements of opium in its other forms, that physicians, little knowing what they were about, took readily to the syringe in whatsoever sort of patient, and actually, indeed, handed over the use of the instrument to nurses, even to the patients themselves: many persons were thus led by trusted advisers into temptation who would otherwise have been clear of it.

Nowadays whoso betakes himself to the morphine syringe does so of his own naughtiness; yet that there is a good deal of such naughtiness in this world may be inferred, not only from personal experience, a fallacious guide, but from the huge consumption of the drug. For instance, during the twenty-five years beginning in 1854 and ending in

1880, the quantity of opium imported into the United States increased from 72,000 lb. to 372,000 lb.; the population during that time, so far as can be gathered from ordinary sources, no more than doubled itself. Now, in its medicinal uses the consumption would not shew a very large relative increase; how then are we to account for so vast a relative increase? The question is a hard one to answer. There must surely be a considerable increase in its use outside the sphere of legitimate medicine; and we may suppose that the use of morphine as a self-indulgence accounts for a good deal. The proper medicinal uses do, no doubt, increase with the greater demand for skilled medical assistance which comes with greater wealth; yet the increase seems more than any legitimate demand can explain. That the drug is used largely as a means of self-indulgence cannot be doubted by any medical man of experience.

Now, who are the persons who thus indulge themselves? The prompt answer will be—the neurotics. Who, then, are the neurotics? We are all said to be neurotics nowadays. Quickness and sensibility, acute perception, and alert muscular reaction are not morbid characters, but qualities of high breeding; these qualities, however, become morbid when they are developed in relative excess in the lower ranges of sensibility, that is, the higher qualities remaining at their former mean the controlling centres can no longer hold the lower centres properly in check. Now, that which in higher centres we call control, and in the lower inhibition, consists in the reverse of this—in the cultivation of the higher planes of thought and sensibility, whereby the activity of the lower is not so much diminished as transformed. Unfortunately, disease may reduce a man to the level of those who had never known a higher state, and a man of mobile and sensitive fibre may thus for a phase become a neurotic: such a one may also become a morphinist under the pressure of pain or other distress, but he is not to be spoken of as constitutionally a neurotic. Again, not a few elderly persons have been under our care for sciatica, post-herpetic and other neuralgias, and the like, for whom morphine injections had been used; from such sufferers, however, this means must be firmly withheld, for it brings them into this dilemma, that while to break the habit is in later life a harder task, its continuance, by the cachexia it produces, is in them more quickly injurious to health than in younger persons. The establishment of a morphine habit in old people too often means an inevitable bondage, and shortened and fretful days.

Another class of patients—not neurotic—presents itself to our consideration, namely, of those, young or old, who, smitten by incurable and painful disease, expect no long span of life. Do we rightly encourage in these the use of the morphine syringe? That in some such cases, as of aneurysm, for example, the practice may be the lesser of two evil courses, may well be; but the solace is purchased at a heavy price. Whether pain soothed by less treacherous means be better, not only for the patient's friends but also for himself, than tearfulness, petulance, caprice, and a deterioration of character, which make the death-bed a scene of pettiness

and exaction, rather than an example of fortitude and serenity, must be decided in the individual case. However, in some such instances the use of morphine may be the only alternative to pain, spasm, or agony, otherwise not to be borne.

Not a few persons are led into morphinism by pain which is wearisome rather than acute. A remarkable instance of this kind of temptation was long under our observation. A business man of middle life, refined and intellectual but not to be called neurotic, who used his morphine syringe with unusual self-restraint, never perhaps beyond the measure of half a grain thrice daily, told his medical advisers that a wearing pain in the epigastrium deprived him of all pleasure, or even of capacity for life in business or society. In order to discuss an important matter with a customer he must inject morphine, or be unable to give his attention to the matter in hand. His abdomen was examined with negative results. We were tempted to suspect him of hypochondriasis; and, in spite of his economy in the practice, his life fell slowly to a lower plane. He got sallower, thinner, rather fretful, and at last, as is often the case in morphinists, he was suddenly overborne by an attack of acute disease of no great severity. A necropsy shewed a band of about an inch in length attached by one end to the walls of the abdomen, and by the other to the anterior wall of the stomach. This being in the very spot to which he had always referred the pain, there was little doubt that its cause was thus discovered. The band had probably arisen as a consequence of an ulcer of ancient date; but such draggings, whether due to slips, scars, or bands, may be the cause of morphinism in persons not more neurotic than the rest of us. A dragging of this kind may be at least as hard to bear as acute pain, which usually presents long periods of remission.

Again, a drag on the mind may act like a drag on the body. Sheer ennui, a luxurious life with nothing to feed the mind or fortify the temper, may lead to the vice. Want of exercise, over-eating, incessant and trivial social claims and emulations, with the disappointments, fatigue, or dyspepsia they produce, may be efficient causes of morphinism. Let a passing pain attack such a person, and therewith perhaps an unusual call on the energies, and to one thus driven and embarrassed an immediate relief suggests itself,—just this once, this one draught of brandy or ether, this one syringeful of morphine; there will be little interest to pay on so small an advance. These victims must be many.

Then comes the troop of those "neurotics"—persons subject, perhaps, by nature to larger oscillations of nervous balance than the normal man —who scent intoxicants from afar with a retriever-like instinct, and, curious in their sensations, play in and out with all kinds of them; narcotics possess such folk almost by anticipation, and they often find less difficulty in the first tolerance than other people. With conscience blunted, and the bit out of the mouth so that energy is set loose as it never was before, energy expanding under no self-criticism, energy joyfully soaring into extravagance with that bemused sense of brilliant ascendency which animates the "general paralytic" in his earlier phases

—be it morphine, alcohol, chloral, cocaine, all or any are welcome: the intoxication with its hours of excitement and repose must be had at any price, and every reform is followed by a relapse into the use of the same drug or of another. It is in these persons that a hereditary craving for intoxicants is found; and with this tendency we may find in the family tree nervous disease or insanity; yet by no means always so. Individuals of such families, indeed, may naturally possess great intellectual powers, and may create splendid waking dreams out of drugs and wines which fuddle the rest of us—though it must be admitted that the records of these fantasies rarely bear out their report. It is curious to see how soon these persons become aware of their capacities, and even in their adolescence find their way to such potions as little ducks to the water, under however dry a hen they may have been reared. Gambling seems to break out in some persons in the same irrelevant way.

There is still one more group of morphinists, those who take to morphine on small excuse because it lies to their hand. Of these weak persons doctors and druggists form the majority; the rest are chemists and other men of science familiar with such means, who think in their folly that their technical knowledge will give them the use without the abuse of them. Unfortunately these very persons in their conceit become the most abandoned and, their opportunities being continual, are the least reclaimable.

In respect of sex there does not seem to be much difference; the anticipation that the practice would be found more prevalent in woman is not supported by facts.

The habit may be acquired at any age after the escape from tutelage into the temptations and cares of the world. When the practice is begun in advanced life, pain and medical or quasi-medical advice may give the cause and the opportunity. The morphine habit is rarely or never known to be established under the weight of bereavement or other such heavy trial; alcohol or chloral seem to be preferred by those who cannot wait for the healing hand of time.

On the other hand, morphinism often arises from some discomfort or disorder following parturition. The syringe should never be used, not even in the hands of the physician himself, in cases of uterine disorder; slower but safer means of cure are to be found.

The total daily quantities of morphine which may be used by morphinists vary largely. In our experience about fifteen grains seem often to have been the ordinary daily quantity, to be run up, if a servant give notice, or other real or imaginary worry occur, to thirty, or perhaps even to forty grains in the twenty-four hours. Other writers speak of quantities so large as sixty or seventy-five grains in twenty-four hours; on the other hand, some persons, none the less enslaved but with more self-control, keep the daily allowance down to two or three grains: morphinists who have relapsed after cure frequently manage to restrain themselves to smaller quantities, but too often by bringing in the supplementary aid of alcohol. Old persons, who in relief of some

malady have fallen into the habit, seldom receive more than one or two grains a day, in repeated doses of a third to half a grain; but such persons are usually under some oversight and control. In making these estimates, however, we must not forget that the morphinist is so ready a liar that his assertions cannot be accepted without corroboration.

The symptoms of morphinism in the earlier stages of the habit are rather moral than physical. The stigmas of a morphinist are plausibility and disorderliness; and by these he may be known. Like certain other sinners who shall be nameless, the morphinist is ablaze with schemes for the benefit of his household, his parish, his country, and the world. He is usually a clever, and often an interesting person, sometimes even endowed with a rather "damaged" kind of genius; but owing to the perverseness of circumstances, nothing ever comes off. So perverse are things, that if one did ever indulge a taste for drugs, the occasional aid—just for a week or two till things are straight—should be regarded as a venial matter, if not justifiable. If the patient come to the physician, he will have had a dose within an hour; his pupils are contracted, he is voluble, ingenious in promises and excuses, and very tiresome. He is an hour late for his appointment, owing to the faults of others; if you call on him, you are kept waiting for as long a time as you choose to be detained. If he can avoid it, you do not see him in his ill-humours—querulous, exacting, slanderous, false, as he is in his domestic circle: yet the morphinist is never so lost as the alcoholist; his brain is not fuliginous; on the contrary, for some little time, the length of which depends on the economy of the drug, it is brisk enough. While the stage of elevation continues he is capable of doing a good spell of work in a spasmodic and irrelevant way; therefore, although slovenly, he is not chronically dirty, like a drunkard, but is capable once or twice a week of a good washing; and owing, perhaps, to an insensibility of the skin, his desire for "fresh air" is inordinate. A lady of this kind may come to a ball very smart indeed, though she will arrive when the rest of the world is departing. Her carriage was probably ordered for a drive at four o'clock, and she started at seven, astonishing some new friend by calling at an inconveniently late hour; she dined at 9.30, and arrived at the ball after midnight. In the morning to dress is impossible until the syringe has been used, and she is finally got to breakfast when the rest of the world is at luncheon. In the midst of all this ruin of time she stands complacent as the one faithful in a froward world. Meanwhile, no one can conceive how inconsiderately every one has acted to her, or wonder that occasionally, when thoroughly exhausted by her sufferings which are indescribable and her labours which are prodigious, she should use a very small and occasional dose of morphine. The only truth she tells is that at odd moments she makes great efforts, efforts too often, though by no means always, ill-directed or futile. This utter disregard of time is a marked feature of all users of narcotics, and of morphinists especially; so consistent are their inconsistencies of time and place, they almost succeed in throwing disorder upon the revolutions of

the sun. Dilatory they are, even more are they diligent in contraries—ὁμαλῶς ἀνώμαλοι—turning night into day with a topsy-turviness worthy of Lewis Carroll.

The falseness of a morphinist cannot be glossed over as oblivion; though in part it may be that "Bemused in wine the bard his duns forgets, And drinks serene oblivion to his debts." The finer lines or, for that matter, the graver lines of ethical conduct become so blurred that the victims cease to regard them; thus their mouths are filled with falsehoods; and if confronted with proofs of falseness the morphinist flippantly ignores them, or says he is driven to prevarication by the nagging or bullying of his friends. It is idle, of course, to argue with a patient with whom we have no common standard of veracity; and to economise his sins it is better in all such cases never to ask a question of a morphinist which requires a serious answer; or at any rate never to give any weight to the answer.

Thus far, then, the symptoms of morphinism are concerned rather with morals and conduct than with bodily disease. But if the habit be continued and the doses increased, as will be assuredly the case and that quickly, symptoms of bodily disease will appear; say in six or eight months at farthest. The flesh begins to fall; the face loses colour and takes on a sallow, lustreless hue and an aged expression; the teeth are loosened, and gradually even a young person becomes wizened, emaciated, and haggard. To this rule there are some exceptions; a few patients keep their flesh, or even grow fat and puffy: such persons are good feeders, take wine freely, and probably escape the catarrh of the stomach which attacks the greater number of their fellows. Constipation is always present, often in most obstinate degrees; the mouth is parched, and other secretions as a rule are arrested; though some morphinists sweat profusely. Still, for many years life goes on, and the constitution does not break up: morphinists do not, however, live to full age; and, if the habit be contracted in old age, the patient fades away in no long time. In younger subjects the social affections grow cold; waywardness and caprice deepen into selfishness and physical and moral degradation: the fitful charms of character or the powers of mind, if any such there were, are blotted and spent; memory especially fails; amenorrhœa and sterility overtake the woman, and impotence the man; irregular febrile attacks appear; albumin may be found in the urine; even sleep is heavy, or is exhausting and disturbed by hallucinations; abscesses arise at the punctures of the unclean needle, and heal badly; the mouth is dry; the teeth decay; gastric catarrh increases, with symptoms of nausea, retching and flatulence, and of an epigastric or substernal pain which is rather too characteristic of morphinism to be put down merely to the catarrh:[1] the thread of life grows frailer; all capacity even for fitful work disappears; the intercurrent miseries of the habit are intensified, the moments of excitement briefer and less effectual, until

[1] Hitzig says that in morphinism hydrochloric acid fails in the gastric juice, and that the cravings are due to returning acidity.

the patient curses the day he was born: in later middle life at farthest he dies, usually cut off quickly by some chance malady.

Pathological Anatomy.—Autopsy is rare in cases of uncomplicated morphinism. The only important point herein is the state of the heart. Schweninger and others allege that fatty degeneration of the heart is to be found in these cases after death. On clinical grounds we have seen no reason to suspect its presence, either in the course of the malady or in a prevalent mode of death. And the testimony of the best authors seems opposed to the belief that fatty heart is a direct consequence of morphinism. Wittkowsky's papers are helpful in this aspect of the matter. It has never yet been shewn experimentally that morphine has any direct action on the heart. The observations of Binz on the fall of blood-pressure in acute poisoning of animals by morphine have little bearing on chronic poisoning.

Diagnosis.—Chronic poisoning by chloral or the bromides may be difficult to distinguish from morphinism; but the diagnosis would rarely be of urgent importance. In poisoning by bromides these bodies may be found in the urine and often in the saliva; in chloral narcosis the chloral may be detected in the urine either alone or in combination with glycuronic acid as urochloralic acid. A difficulty may arise in a case of delirium in a patient previously unknown to the physician. Morphine delirium may resemble delirium tremens or mania. Scars on the skin should be looked for. The tremors in morphine delirium increase with the delirium, in alcoholic delirium they decrease. Morphine delirium may occur as well in women as in men; and women may present hysterical features, such as contractures, screams, or catalepsy. Albumin may be found in the urine in either delirium, but more frequently in the alcoholic form. The hallucinations in morphine delirium are less revolting, and its duration is rarely more than thirty-six hours. Finally, in this malady a morphine injection will probably give prompt relief. The history and character of the attack generally suffice to distinguish it from mania.

The diagnosis of a secret morphine habit is very difficult. Periods of excitement associated with contracted pupils will usually lead to a correct conclusion; and the patient is pretty sure not to face the doctor without a dose. An excuse may be made to examine the arms, when scars may be found. Still this opportunity may fail and diagnosis be impossible without seclusion. Seclusion for twenty-four or thirty-six hours will certainly betray the craving.

Dr. Mattison has reported more than one case in which this habit was practised by a wife for years without the knowledge of the husband. That such instances can be cited is of medico-legal importance.

Prognosis.—If the habit be broken off, the constitution, even in severe cases, will appear to have undergone no profound deterioration: and the patient may regain all or much of his former health. The forecast in extreme cases must be estimated in accordance with the special characters of each. Authentic cases are on record of morphinists or

opium-eaters, abandoned to the habit for twenty and even for thirty years, being cured completely by these methods, both in mind and body.

We have not found insanity to be a consequence of morphinism, save in persons in whom insanity was already potentially present. In persons with such a proclivity an access of insanity may be hastened by any reducing cause. Occasionally, however, insanity follows the use of morphine more directly, and if so, it usually takes the form of mania of persecution; the backbiting of friends, which is a common symptom in ordinary cases, becomes more extravagant and persistent. Except on withdrawal of the drug we have not seen the excitement or violence to which the name morphinomania would be properly applied.

In one or two cases of morphinism which have come under our notice the patient has died suddenly and unexpectedly; the presumption is no doubt that such deaths are due to heart failure. Relapses after apparent cure occur in about 70 per cent of all cases.

Treatment.—There is one means of dealing with morphinism, and one only: namely, seclusion in a special retreat, and submission to the discipline therein provided for such cases. Cures have occasionally been effected by home treatment; but the enormous difficulties of curing the habit, if once it have hold of its victim, need no emphasis. A wife can have no control over her husband, nor contend against a stronger will clad in the armour of deceit; a husband has not the fortitude to turn a deaf ear to the terrible cravings and perhaps recrudescent neuralgias of his wife. No nurse, no medical man can keep up authority or carry out plans in such cases, without being overborne or deceived. A physician of mature age and experience cannot attend upon such patients without intermission; a young resident physician soon becomes powerless. Their wiliness is marvellous, and, under the most frank seeming, deception is surely at work: the physician may be certain that a tractable subject is getting the drug on the sly. We have stated that after hypodermic injections nearly 70 per cent of the morphine is excreted in the fæces, but this large amount holds good only for acute poisoning; in chronic poisoning it is very much reduced, and if the system is very tolerant it may be almost absent, the tissues appearing to oxidise the drug in much the same way as they oxidise fat. Very little morphine is at any time excreted by the kidneys. It is therefore evident that we cannot rely on the detection of morphine in the urine to tell us of the secret habits of our patients.

The physician is doing no kindness to the patient or his family if he trifle with the duty of insisting upon prompt seclusion. The patient himself will probably protest loudly; he dreads the horrors of the withdrawal, especially if he has been "cured" before; in spite of his better judgment he clings to his indulgence, and he harbours dreams of curing himself on the coming of that golden time when the trials of his world shall cease. Moreover, many such patients honestly think that the shock of withdrawal would be more than in their weakly state they are able to bear. To all these pleadings the judicious physician will lend no ear;

he cannot, nor can any friend compel the patient to go into seclusion; but there are many material arguments which can be brought to bear upon a weakened will, not without success: moreover, the patient in nearly all cases is secretly desirous of escaping from his bondage—if it can be done without too terrible a wrench. If there be any local disease, such as uterine disease, renal or biliary calculus, as a source of pain, the utmost that can be done to relieve the condition must be done before the cure of the morphine habit is taken in hand; or the cure may fail under the pressure of recurrent pain. It is desirable to warn the friends of the sufferer beforehand that the period of detention, or at any rate of removal from home, may be as long as twelve months; but the time of probation can be better discussed when the means of cure and the tendencies to relapse have been considered. The first part of the cure is, of course, the withdrawal of the drug; and it is convenient, therefore, now to describe the

Symptoms of Withdrawal.—In order to understand the cravings of the morphinist after the morphine has been withdrawn, it is necessary to appreciate the manner in which the drug satiates this appetite. Morphine, as we have already pointed out, has a specific action on sensory nerve-cells; the exuberance of imagination, the wandering mind, and the rapid flow of ideas represent the general exhilaration of intoxication caused not by direct stimulation of the brain but by loss of guidance of the trains of thought by the controlling centres. That the higher centres are certainly not stimulated at any period may be tested by the performance of elementary mental efforts such as choice-reactions or adding up rows of figures, the time of which is always increased. Later in the intoxication the afferent impulses to the lower centres of the brain in their turn are blocked; the patient becomes sleepy and the reflexes disappear. When the action of the morphine wears off the contrary conditions obtain, the sensory nerve-cells after their prolonged rest are hypersensitive in much the same way as when on awakening from a sound sleep our eyes are at first hypersensitive to light. Moreover, it can be definitely proved in the lower animals that morphine and its allies in the second stage of their action, that is, when the depression is beginning to wear off, produce an effect on the sensory nerve-cells precisely analogous to that of strychnine, but with this difference, that whereas the action of strychnine is mainly upon the sensory cells of the cord, that of morphine is mainly cerebral; nevertheless sufficiently large doses of morphine may give rise to characteristic strychnine-like convulsions (W. E. D.). We conclude then that during abstinence the sensory cells of the morphinist are hypersensitive; and, further, as it is the highest or psychical centres which are mainly affected these will be principally concerned in exaggerated function. Thus, an ordinary sensation when converted into a perception is exaggerated out of all proportion to its importance, and the patient for the time being is the victim of these excessive stimuli. His reflexes are therefore exaggerated, but especially are the higher or

psychical reflexes increased; and, as all consciousness is awakened by perceptions arising peripherally as simple sensations, so all cerebral activity must be increased. This hyperexcitability affects the medulla, and so induces vaso-constriction with a rise in blood-pressure, and an augmentation of respiration. Just as the nervous man has a high blood-pressure and the casual or the happy-go-lucky a low blood-pressure, so we find that during abstinence from morphine the morphinist has a much higher pressure than when satiated with the drug.

The chief and most grievous symptom is the dangerous collapse which may follow withdrawal, and if the withdrawal be sudden it may reach an alarming and even a fatal degree. If the drug be wholly withdrawn at the beginning, an anxious restlessness with irresistible yawnings marks the approach of the time of craving; the patient begins to pace the room in a state of tremulous excitement, which becomes an agony; he springs sleepless from bed, he is shaken by rigors, sweat stands upon his skin, and saliva runs from his mouth. Feverless chills and creepiness, or sharp accesses of pyrexia often simulating ague, sneezing fits, deathly pallor, sinking, nausea, and hiccup are attended or followed by vomiting and diarrhœa; the pupils widen, and are sluggish in their accommodation; speech and even gait are as if palsied; hallucinations of vision, of hearing, and even of smell, take possession of the mind, and pass into a delirium often so violent that the cautious attendant will take care that razors and garters have been removed, and the windows secured: it is at this stage that collapse may set in. It is hardly necessary to point out that collapse may arise from any peripheral stimulation provided it be sufficiently severe. A small burn, for example, may do no more than raise the blood-pressure and stimulate respiration reflexly, but a very severe burn has just the opposite effects; it inhibits cerebral activity so that respiration becomes extremely shallow and the blood-vessels dilate. Hence all the blood collects in the abdomen, and although the heart may continue to beat well, it beats ineffectually, for most of the blood is lying in the enormously dilated splanchnic vessels. Collapse may come on unexpectedly even if diarrhœa has ceased; the patient becomes faint, the face pinched, and the voice hollow; the limbs may twitch; the pulse ceases at the wrist, and the signs of consciousness fail. This threatening condition may last even for an hour, or may be repeated again and again within the day. If the ordinary cordials fail to put off the danger the injection of a small quantity of morphine never fails to do so. Clearly the collapse is no mere consequence of the vomiting and diarrhœa.

As the sudden withdrawal of morphine is no longer practised this collapse may pass out of observation. Levinstein in Germany, and Professor Allbutt in England, formerly advocated sudden and complete withdrawal, partly because it appeared more cruel to protract the misery, as it is more cruel to pull out a tooth slowly; but chiefly because, in the absence of homes for isolation, it was important to get over the crisis before friends or patient should have time to interfere or repent. For

the arrest of the habit once made the chain for the while is broken, and the danger of relapse is not so immediate as in the case of alcohol. Withdrawal once effected, temporary recovery at any rate is assured.

But if the patient can be consigned to a home where there is no danger of interference with the regular progress of treatment, a more gradual although still expeditious method is preferable. A sudden withdrawal is not only more dangerous to the patient than a method which, though rapid enough to end the trial quickly, is not sudden; but also convalescence may be made more tedious by the heavier stress of the sudden method on the sufferer; and some symptom, such especially as diarrhœa, may persist, and prevent complete recovery. The advocates of the rapid (not sudden) methods allege, moreover, that collapse never occurs except on sudden withdrawal. If this be so, it is needless to say that sudden withdrawal, save in mild cases, should be abandoned. Assuming, then, that we are not obliged to snatch our victory, and that the patient is secure in a kindly home, we should prefer the modified but still rapid method as practised by Dr. Mattison and other experienced physicians of these institutions.

If the habitual quantity be small—by which we mean not more than three or four grains a day—the withdrawal in men may be sudden, and the matter thus settled off-hand. In women or shattered men a little more caution is necessary. Again, if the quantities be more than five grains a day, but the patient on the hither side of cachexia and emaciation, some briskness of reforming zeal may be justified, and the enemy expelled without much parleying. But in the case of those who have abandoned themselves to large doses, and are often cachectic, and brought low in nutrition and strength, the physician, after learning, so far as may be possible, the habitual doses and the customary hours of indulgence, may administer during the first twenty-four hours one-half to three-quarters of the usual quantity. Halving this again and again, in five to ten days the doses may reach the vanishing point. Although in some measure the usual hours of indulgence are to be observed, especially the last dose at night, yet the number of injections should be reduced as well as the total quantity of the drug. There is always considerable difficulty in withdrawing the last two or three grains. The patient who may have submitted patiently to the earlier treatment now feels his loss more acutely, and it is at this stage that relapses are most to be feared. Some physicians prefer to substitute opium for morphine, and while so placating the patient reduce the number of morphine injections, sometimes indeed replacing these by injections of other narcotics. Thus, Dr. Burkart takes several weeks to reduce the morphine and afterwards substitutes opium for it. Dr. Jennings diminishes the injections as far as possible without unduly inconveniencing the patient and then, whilst further reducing them, substitutes for them injections of opium by the rectum.

It is needless to say that almost everything now depends upon the tact and integrity of the attendants, to whom enormous bribes may be offered. Nor must they fail in astuteness, for a morphinist is an astute person,

and often has morphinistic or other perverted allies outside the house. The patient on admission must have a bath, in order that all his clothes and person may be searched; he must be taken from the bath into a warm room, in which are none of his own effects; slippers, letters, books, and the like must be minutely examined, or not admitted. Allegations of sleeplessness must be accurately tested by the nurse's record.

By this modified method the accidents of collapse or violent diarrhœa are avoided on the one hand, and on the other we do not drag out the patient's sufferings unduly. Dr. Mattison in Brooklyn, while withdrawing the morphine as quickly as the individual state may justify, gives 30 grains of sodium bromide on the first day to ease off the suffering, and, adding $7\frac{1}{2}$ grains daily, reaches 80 or 90 grains a day as the morphine comes to an end. He then gives 30 grains of trional every night for a week; reduces this in the week following to half the dose, and ends the case with a little chloral hydrate or paraldehyde; and indeed any of the ordinary indifferent hypnotics will no doubt be useful, for by depressing the cerebral centres which are in a state of hyperactivity they will allay the patient's distress. Narcotics should, however, be used cautiously, and the harmful tendency of many of them must not be forgotten. Chloral, for example, is a powerful cardiac depressant, and sulphonal when continuously administered is a dangerous drug and liable to produce suddenly coma and hæmatoporphyrinuria. Codeine and the synthetic morphine compounds, ethyl-morphine (dionin), benzyl-morphine (peronin), diacetyl-morphine (heroin), may be substituted for morphine; and, as they act on sensory nerve-cells in a very similar manner to morphine, they will remove the craving for the latter drug: but this is not treatment; we are only substituting, so to speak, one type of morphinism for another.

Many other drugs are recommended by this physician or by that, as surrogates for morphine after the reduction or removal of the drug—such as chloralamide, trional, monobromide of camphor, and so forth. Hyoscine is an alkaloid which has lately come much into use; treatment of morphinism by this drug was originated by Lott, and consists in keeping the patient under its influence for two or more days during which time the morphine is withdrawn. It need hardly be said that hyoscine has no specific action on the morphine craving, and such effect as it has is caused by depression of the cerebral hemispheres, and especially of the motor area. Like all other "systems of cure" for morphinism it has its partisans and opponents. Rosenberger reports a case of a patient who took 60 grains of morphine per diem and was cured by hyoscine; Mattison and Crowthers regard the treatment as both useless and dangerous. Birge relies primarily upon injections of mandragorine (an alkaloid having an action similar to that of atropine) and pilocarpine, the one to remove the craving, the other to aid in the excretion of the morphine; the patient is kept under the influence of these two drugs for about 72 hours, during which time no morphine is administered. This treatment is clearly based on a misconception of the situation. The

craving, as already mentioned, is caused by hyperexcitability of the cerebrum, and for this there can be no specific treatment except in so far as depression of cerebral cells may be regarded as such; moreover, it is difficult to see how the pilocarpine can be of value by aiding the excretion of the alkaloid, because we know that in the case of the habitué the morphine is not excreted but is destroyed in the body. Hoffmann recommends camphor as a specific; he says it antagonises morphine by producing vaso-constriction and a rise of blood-pressure: it is hardly necessary to point out that camphor has no such action.

Dr. Jennings adopts the slow plan of treatment with the substitution at a certain point of rectal injections for hypodermic. He uses also "cardiac tonics" to combat depression of the heart, alkalis for the hyperacidity, and Turkish or hot-air baths. For our part we would not place undue reliance on any of these measures. It has never been shewn that morphine has a direct action on the heart, and certainly the sphygmographic tracings produced by Dr. Jennings do not shew it; all they shew is a high blood-pressure, which, as we know, can be lowered by nitrites, morphine, or sparteine. Furthermore, sparteine is not a cardiac tonic as he suggests; it acts by depressing certain nerve-cells in the body, and any effect it may have on the heart is towards depression, that is a diminution of cardiac output per minute. Dr. Jennings and, later, Erlenmeyer have employed sodium carbonate for the gastric symptoms which may be so distressing during the treatment; symptoms which they attribute to hyper-secretion of acid into the stomach. We find caffeine most useful in combating syncope or collapse. For the same purpose copious hot-water enemas (105° F.) are useful and seem to soothe the diarrhœa. If the stomach be so disturbed that absorption is likely to be slow, then no doubt it is better to inject the caffeine. It is well also to throw hot strong coffee into the rectum. The bromides, in our experience, are chiefly useful at the periods of excitement; but it must be remembered that we are but substituting one sensory depressant for another, though with this difference, that whereas morphine acts upon the sensory cells in an evolutionary order, the bromides obey no such law, but act upon the higher centres, the motor area, and the medulla at one and the same time. Graduate the descent of the doses of morphine to the vanishing point, and make the transition in the individual case as rapidly as the constitutional state and the grain of the habit will permit; but beware of teaching the patient the use of a new narcotic. Cocaine, which has been recommended as a temporary substitute, is a most mischievous agent, and is carefully avoided by all physicians who have experience in these conditions [see "Cocaine Poisoning," p. 968].

Whatever the value of auxiliary drugs, the importance of nourishment is much greater. Without the utmost care and urgency in feeding, the most promising cases may do ill. The dietary must be of the most generous kind, as the stress lies heavily upon the pined body. The gastric catarrh, perhaps always present in a greater or less degree, is

a serious interference with this purpose. When the nausea and vomiting are troublesome, cold meat-jellies, iced coffee with or without cream, iced champagne, and the like, must be tried by the mouth, and supplemented by nutritive enemas. As the stomach becomes more capable of work, turtle and other strong soups, and like generous and restorative foods, must be pressed upon the patient; and gentle massage used to promote absorption and blood-formation [see art. on "Massage," Vol. I. p. 433]. The alcoholic remedies must be used sparingly, and omitted as soon as possible. As convalescence advances the nutrition very rapidly improves; massage may be more freely used, tonic douches carefully administered, and drives in the fresh air provided, which are better than bodily exercise; the massage produces as much muscular movement as the patient can bear without fatigue. It is said that cases of "hysterical neurosis," combined with morphinism, are often cured in this process of withdrawal which, indeed, in the latter parts of it, differs little from the method of Dr. Weir Mitchell. It is stated by several authors that on withdrawal of the morphine the sexual appetite, long in abeyance, may return vividly and even uncontrollably. It is therefore of the utmost importance that women should be attended by mature nurses of their own sex, and men by male attendants only.

It has been but too often our misfortune to see the pains which led to the morphine habit return with the suppression of it; a most disheartening event. In one of these cases the patient was an old gentleman of seventy years of age; the other a lady not in a retreat, and not submitted to special feeding and massage. She remained emaciated, and, as her sufferings were renewed, her friends had to acquiesce in her return to morphine as the lesser evil of the two. The patient was not under full control, and the case occurred before Dr. Mitchell's method had attained its present beneficent vogue. During the last twenty years we have all become more alive to the truth that in thin neurotics, whether submitted to formal seclusion and massage or not, the first duty of the physician is to press nutritious food upon the fastidious patient until a substantial addition to the bodily weight is regained. With our riper experience we may now be assured that, if restorative treatment be persistently carried out, these recrudescent pains will gradually disappear again.

After-treatment and Relapses.—We have spoken of seclusion, or at any rate of absence from home, so long as a year or a year and a half. How can this be necessary when the withdrawal is completed even in a week or two, and the craving summarily overcome? In dealing with this part of the subject we have to speak first of the disposition to relapse; for it is upon this disposition that the insecurity of the results obtained by the above methods depends. On the whole, our own cases have shewn no inevitable tendency to relapse. Setting aside half-witted and semi-insane morphinists, and a few cases, treated in the past with less determination, in which returns of pain forced the sufferers again to summon the treacherous familiar to their service, the good results of the cases weaned under our observation, or within our knowledge, have been almost always

permanent. In this respect our personal experience of morphinism has been far more satisfactory than of alcoholism; and we have too often seen a reclaimed morphinist become more or less of a tippler. Still we are bound to admit that published statistics do not bear out the permanence of the cures. In Germany the results seem to be less permanent than in England. Of 82 patients recorded by Levinstein, 61 fell back; 28 were women, of whom only 10 fell back—which speaks well for that sex; of 32 doctors, 26 fell back, an awful revelation of our frailty! Oppenheim also refers to the large proportion of backsliding doctors—male or female; in his figures 93 relapsed out of 250. Of 100 males in his series 42 were doctors; next to these came apothecaries, chemists, druggists, and others who by their calling are familiar with drugs, and in possession of them, and of the means of their use. In a paper read at the meeting of the American Medical Association at San Francisco in 1894, Dr. Mattison reported that of 300 patients 118 were medical men; and, in another set of figures, 62 out of 125 were of our profession. We must admit, then, that of the backsliders our own profession furnishes a large proportion. So far as personal impressions may go without figures we find our own experience to point in the same direction; though we have seen several good cases of permanent cure in medical men: even medical morphinists are not to be without hope. Prof. Osler's judgment is that the morphinist is "only too apt to relapse into the habit." Our own impression is that if the alcoholics and wrecks of other sorts were separated from the heap, the record of permanent cures would stand far better than these figures indicate, figures which, properly of course, include morphinists of every kind and degree. In the case of a respectable sinner with good home, and friends to help him, we think a favourable prognosis may be given if after four or six weeks' residence in a retreat, according to the severity of the case, certain precautions, such as we now set forth, be carefully carried out.

The After-cure.—All observers experienced in morphinism are agreed that, unless circumstances forbid it, the patient, after the withdrawal is established, say in two or three months, should take a sea voyage. Not the body only but the mind and ethical habit of the patient have to be remade. Erlenmeyer well points out that of the many grave objections to a slow tapering off of the doses of morphine, not the least is the waste of valuable time which ought to be given to the after-cure. A personal medical attendant is not usually necessary if the health be restored; all well-found ships have a medical man on board, who must be made aware of the former habits of the patient, and be warned never on any pretext whatever to permit the patient the use of narcotics of any kind, or to administer them himself, except in some extraordinary circumstances. The voyage should last for some months. The travelling companion must be a person of some ascendency over the patient, whose will indeed is usually weakened by his previous excesses; and to him a grave warning against alcohol must also be given, for until their morale

is restored these dilapidated creatures, if they do not relapse into morphinism, often fall under the bondage of drink. If a sea voyage be out of the question some means must be found of establishing the patient's health while protecting him from that contact with the stress and harshness of the world which he cannot bear until mind and body are thoroughly restored. During this interval douches and other corroborants must be employed in order to steady the nervous system. But the cares and stress of the world are not the only stones of stumbling. Paul Sollier has described certain tides of recurrent craving which beset the convalescent; for twelve or eighteen months after the cure, Sollier says that crises may come on, lasting for twenty-four or thirty-six hours, during which time the patient is possessed by a sense of intolerable weariness, dyspepsia—shewn by flushing after meals and loss of appetite—sluggishness, and even diarrhœa and "biliousness." That this is more or less true we can aver, though we have not observed these systemic fluctuations so accurately as Sollier has done. The times of trial presumably begin as overwhelming psychical yearnings, and take their origin in the nervous system, the gastric and other symptoms being secondary to the nervous perturbations. However this may be, we know that such a recurrent strife may be the lot of the patient for a year or more after the weaning; and herein lie the reasons for advising a long tutelage, unless the patient can be carefully watched by his friends. If the patient have no judicious friends to secure him against these resurgent tides of temptation, a long residence under the discipline of an institution may well be necessary.

It has been held by the courts of the United States that addiction to morphine, even in great excess, is not sufficient alone to prove testamentary incapacity. So far as we are aware, the question has not arisen in the English courts.

Hypnotic suggestion has been recommended as a cure for morphinism. Though without any personal experience of the method, we have taken some pain to discover its virtues. So far as we can judge, it is in mild cases only that this remedy has had even an appearance of success; and to send a patient quickly out into the world again under "suggestion" is to court the failure which will probably follow.

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On some other Intoxicants

Hasheesh Poisoning.—Cannabis Indica is an example of a plant which yields a toxic substance only when grown under definite conditions. In Siberia it is not toxic; but in India the resin which is elaborated and utilised for the growth of the seeds is found to be poisonous. The active principle is an oily substance which can be removed from the resinous material by petroleum-ether. This oil, cannabinol, is remarkable in that it contains no nitrogen; it readily loses its activity on exposure to air as the result of oxidation. Hemp-resin of different seasons and places contains a very variable amount of cannabinol, so that the amount of resin forms no criterion of the toxicity of the drug. And, as the amount of cannabinol cannot as yet be estimated chemically, we have an explanation why so many of the galenical preparations on the market are valueless. The drug, as prepared in India, is known in three forms: bhang, the dried leaves of either sex; charas, the resinous exudation; and ganja, the dried flowering tops coated with resin. The term "hashish" or "hasheesh" is a collective name applied indiscriminately to all parts and preparations of the plant. Hemp may be administered either by the mouth, when its effects are apparent usually in from a half to three-quarters of an hour; or the drug, generally as ganja, may be smoked, when the symptoms come on almost immediately but do not last so long. The action of Indian hemp is upon the brain, it is both a deliriant and a soporific. In small or relatively small

doses it gives rise to gay hallucinations, at any rate in some persons and races; it is also said to act as an aphrodisiac, the dreams being of a lustful kind. To Europeans, however, this description scarcely applies; the dreams are simply disagreeable. The first effect of the drug is to produce excitement which is comparable in many ways with that seen after taking alcohol: the patient is noisy and restless, he is less shy and freer in speech, he laughs immoderately at trifles, and his manners are abandoned and no longer conform with those of polite society. As in the case of alcohol we believe that this excitability of the motor areas and lower centres in the brain is not due to direct stimulation, but to depression of the highest and controlling centres. Certainly there is a depression of the highest centres during this excitement, and this is shewn by diminished capacity for the performance of mental work, inability to concentrate the attention, and by feeble judgment. Nevertheless, as in the case of the alcoholic, the patient regards the drug as a decided stimulant, and his uncontrolled fancies he looks upon as the cerebration of an exalted brain. It is of course needless to state that the testimony of introspection during this condition is worthless as evidence of stimulation. If the environment be suitable the patient sooner or later sinks into a condition of dreamy and languid contentment followed by sleep. Hallucinations and delusions form a characteristic feature during this intoxication. Ideas of a more or less impossible sort flicker across the mental horizon; the patient does not recognise that they are ridiculous and is quite unable to control them. Of these the two most important illusions are those of time and space. Time is estimated incorrectly, minutes appearing as hours. It should be remembered in this connexion that we estimate time by successive mental impressions: and the uncontrolled and fleeting thoughts and impressions obtaining during hemp intoxication may well lead to an overestimation. Space also may be overestimated, although this is less common. These illusions are seen in other forms of intoxication also, for example, in that of morphine and mescal, but in the case of hemp they are more pronounced. Certain physical signs are also evident during hemp intoxication, such as muscular weakness, inco-ordination of movements, and slurring speech: thus hemp is contrasted with morphine, which in moderate doses has no effect on the motor functions. Like morphine, however, hemp diminishes the perception of pain and induces a partial anæsthesia of the skin. Early in the state of intoxication reflexes are usually increased, although later they become decidedly depressed.

The effect of the inhalation of the fumes of ganja is to produce an exhilaration and sense of refreshment which are particularly noticeable after fatigue, mental or physical; these feelings are more pronounced than those produced by either tea or alcohol, and are not followed by reaction. In the space of some twenty minutes to half-an-hour the effect wears off. The sensory nerves are benumbed and the pupil is dilated. There are no constant symptoms of respiration, pulse, or temperature.

It is stated by the "Indian Hemp Drug Commission" of 1893-94

that "its moderate use has no physical, mental, or moral ill-effects whatever." "Its excessive use injures the physicial constitution, and may cause dysentery and bronchitis. It tends to weaken the mind, and may cause insanity sometimes. It induces mental depravity and poverty, but rarely crime. The injury caused by excessive use is confined almost exclusively to the consumer, and scarcely affects society." The Commission thought that careful inquiry reduced the proportion of genuine hemp drug cases. "Of 222 cases of insanity ascribed to hemp drugs in the Lunatic Asylum statements of 1892, only 98 are found on careful inquiry by the Commissioners to have any connexion with them. The result is that of the whole number of cases admitted to lunatic asylums (in India) in that year only 7·3 per cent can be ascribed to hemp drugs, and if cases in which hemp drugs have been only one of several possible causes are omitted, the percentage falls to 4·5. . . . Hemp drugs cause insanity more rarely than has popularly been supposed, and the resultant insanity is usually of a temporary character and of shorter duration than that due to other causes." The latest account of hasheesh insanity we owe to Dr. Warnock, and the following paragraphs are extracted from Dr. Clouston's review of Warnock's Report for 1895 in the *Journal of Mental Science*, October 1896 :—

Dr. Warnock had some interesting facts in regard to hasheesh and its mental effects. Of his 253 admissions in the *last* half of 1895, 40 were put down to the abuse of hasheesh, and 40 more to the combined effects of this drug and alcohol. Of 80 cases only 5 were women. In 41 per cent of all his male patients hasheesh, alone or combined with alcohol, caused the disease ; while in only 7 per cent of his female patients was this the case. After stating that the habit of smoking Indian hemp is widely prevalent in Egypt, he asks : "Is there a form of insanity produced by this habit so frequently occurring or of so peculiar a type that it can be demonstrated by asylum statistics ? And is hasheesh a potent factor in the production of insanity in Egypt ?" His conclusions are : "1. I have no doubt that in quite a considerable number of cases here hasheesh is the chief, if not the only, cause of the mental disease. 2. I doubt very much if hasheesh insanity can be at present diagnosed by its clinical characters alone. Many hasheesh cases recover almost immediately on their admission, an abstinence from the drug being in such cases followed by a cessation of the morbid symptoms." This sudden and rapid recovery is the most pathognomonic symptom. He classifies the usual types of hasheesh insanity as being :—

"*a. Hasheesh Intoxication.*—An elated, reckless state, in which optical hallucinations and delusions that devils possess the subject frequently exist. Sometimes the condition amounts to delirium, which is usually milder, more manageable, and less aggressive than that of alcohol, and exhibits none of the ataxic phenomena of the latter. Recovery takes place in a day or two, or less ; and the patient usually recognises the cause of his excitement." In connexion with this "intoxication" Dr. Warnock asks if the subject of it is to be held responsible for crimes committed in this state or not ?

"*b. Acute Mania.*—In this type terrifying hallucinations, fear of neighbours, outrageous conduct, continual restlessness and talking, sleeplessness,

exhaustion, marked incoherence and complete absorption in insane ideas are the prominent symptoms. Such cases last some months, and do not always recover.

"*c. Weak-mindedness.*—With acute outbreaks after each hasheesh excess. These cases are very numerous. While in residence such patients are quiet usually, and well behaved, and only betray the impaired state of their brains by being over-talkative, easily pleased, lazy, anergic, excitable on small provocation, unconcerned about their future, and willing to stay in hospital all their lives. They shew no interest in their relatives, and only ask for plenty of food and cigarettes. After being discharged such cases soon return in a condition of excitement—in fact in a mild form of type *b*. They then talk rapidly and rush about, pouring torrents of abuse on those near them; curse and rave on slight provocation; are sleepless, and for ever moving in an aimless way; are urgent to be released. They deny the use of hasheesh at one moment and boast of its wonderful effects the next. Besides these types there are numbers of cases of chronic mania, mania of persecution, and chronic dementia, alleged to be produced by hasheesh, but I have no means of verifying these allegations."

Cocaine

Cocaine and its salts have been largely used as a means of producing anæsthesia. They have also been recommended by physicians and others as a temporary substitute for morphine in the weaning of morphinists from their habit. The drug has, moreover, been used as a habit for its own sake—either the leaves are chewed, as by the native Peruvians and others, or the alkaloid is taken into the system, by injection or otherwise, in its pure state. Cocaine is derived from the Erythroxylum Coca. The use of it by the inhabitants of the Pacific side of South America goes back beyond historical times; and under the name of "Spadic," and other names, the leaves are largely used at the present day by the Peruvians and other tribes of Western South America. The leaves are chewed and mixed with lime, and, in the habits of those races, they seem to take the place that tea and the like do with us. Under the influence of the drug the Indian is said to perform rapid and long journeys, or to carry heavy loads on very small quantities of food. The abeyance of appetite is probably due to the benumbing effects of the drug on the coats of the stomach. Following the example of Sir Robert Christison, we have carried some coca with us to the Alps on more than one occasion in the hope of humiliating our fellow-climbers by some feats of activity or endurance, but without success; the leaves were obtained from a trustworthy source, but they seemed to have no effect whatever.

The drug as taken by the Indians is said not only to endow the labourer with extraordinary powers, but also to have the cheering and exciting effects of a nervine stimulant. Among these people, however, it is said that those who use coca in excess fall into a marasmus. The Indians say that under the influence of coca they need no sleep; certainly insomnia is one of the symptoms of poisoning by

the alkaloid. It must be remembered, however, that the alkaloid cocaine does not represent the whole action of the leaf; other alkaloids such as isatropyl-cocaine, benzoyl-ecgonine, and some volatile oil are also present and may to some extent modify the action. For the same reason, coca wine should be prepared from the properly preserved leaves and not by the simple addition of cocaine.

The virtues of this agent in producing local anæsthesia are well known. A 2 per cent solution of cocaine painted upon a mucous membrane, as on that of the eye or of the mouth, frequently proves itself a sufficient anæsthetic for superficial operations. By subcutaneous puncturings even a deeper anæsthesia may be produced; but the beneficent virtues of the agent in this direction are unfortunately rendered of less avail by its treachery in others. Cocaine is a rapid and often a deadly poison, and one which has its own incalculable ways with certain sensitive people. Some persons, who are very susceptible to the drug, present no signs of the peculiarity; children, on the other hand, shew a remarkable toleration of cocaine, as to another mydriatic agent, atropine, to which cocaine is allied chemically.

Acute Cocaine poisoning.—So far as we are aware, cocaine has never been used as a means of murder, though a few instances of suicide by the drug are recorded.

Far commoner are cases of mishap in the use of cocaine in surgery. In some of these cases of poisoning the agent was used in careless excess; in the large majority the drug was used in relative excess, no doubt; but the most dangerous use of cocaine is to inject it into cavities, whether natural cavities such as the bladder, the tunica vaginalis, and the like; or abscesses or sinuses, and this is possibly on account of its very rapid absorption. Cocaine is also a dangerous drug to use in the case of broken-down or anæmic persons, especially of persons in whom there is reason to suspect degeneration of the vascular system. The general opinion of careful surgeons and experimenters is, that it is well not only to economise the dose, but also to dilute the solution of the drug to as low a point as 2 per cent. Dr. Hayes reports a case in which the use of a nasal spray in a 4 per cent solution caused delirium and cramps, and Dr. de Havilland Hall a case of poisoning by a nasal spray of 10 per cent. Dr. Mactier reports sharp but transient poisoning, in a man aged twenty-five, by four drops of a 5 per cent solution instilled into both conjunctival sacs. It is probably a good rule never to exceed 3 per cent in solutions for surgical use; yet children are said to tolerate solutions as strong as 20 to 40 per cent (Felizet). Still it can never be wise to presume upon such immunity; for Hayes records the case of a child in which death followed an injection of about half a grain into the urethra. Schede reports grave though not fatal poisoning, in a strong man aged twenty, by the injection of thirty minims of a 10 per cent solution into the urethra; washing out of the urethra and bladder on the first appearance of the symptoms seemed to be of no service. As regards absolute quantities it is very difficult, as we have foreshadowed, to

establish a limit of safety. So little as $\frac{1}{8}$th of a grain injected under the skin has been followed by slight symptoms, and half a grain not infrequently; though this quantity could safely be administered to most persons, and could not be very harmful to any. No doubt such doses disturb those persons only whose susceptibility is high; such persons are probably many, but there is no means of winnowing them out. Ordinary persons can tolerate a quarter of a grain well enough, and even a grain and a half. The reports of fatal doses vary from eight to twenty-three grains (16); Mr. Curgenven records a case in which ten grains were fatal to a woman. One of us once painted his throat liberally with a 20 per cent solution of the hydrochlorate, some no doubt being swallowed. It is doubtful how much of the solution, which contained one grain in all, was used; slight hallucinations and delirium appeared shortly afterwards, though the disorder was not noticed by others.

A widespread anæsthesia can be induced by injecting cocaine into the spinal subdural canal. Complete paralysis quickly ensues below the point of injection, whilst consciousness remains unimpaired; for example, $\frac{1}{6}$ gr. of cocaine injected between the third and fourth lumbar vertebræ produces anæsthesia of the lower limbs up to the level of the umbilicus. The loss of sensation begins in the extremities three or four minutes after injection and spreads upwards gradually. After such injections patients can distinguish between heat and cold after tactile sensations have disappeared. The motor nerves are paralysed after the sensory and recover first, so that the patient may still be able to move his legs when sensation is lost. Pitesci reports 406 cases of spinal anæsthesia without a death. A solution of one-sixth to one-third of a grain of cocaine, made up with cerebrospinal fluid previously withdrawn, was used in all cases. In the discussion which followed Jonnesco reported eight cases with one death, which was attributed to the cocaine. Sevrieana also reported thirty cases with one death. From his still more recent experience of over 200 cases Dickinson says that the method is reliable, and that no anxiety need be felt. Since 1904, however, this use of cocaine has gradually been superseded by the hydrochlorate of β-amyleine, which is usually sold under the proprietary name "Stovaine." Stovaine, when injected into the subdural canal in doses of $\frac{1}{2}$ to $1\frac{1}{2}$ gr., produces a widespread anæsthesia as perfect as that of cocaine. It is reputed to be only about one-half as toxic as cocaine, and to be without the objectionable after-effects of the latter drug. Stovaine is also, to a smaller extent, displacing cocaine as a local anæsthetic: it is an irritant drug, and prolonged application to mucous membranes results in sloughing and ulceration of the parts.

Cocaine, like all other drugs which specifically excite the cerebrum, is a very uncertain drug in its action; the doses for individuals must be carefully approached in each case, and solutions injected under the skin or into cavities must not exceed a strength of 3 per cent: indeed fifteen minims of a 1 per cent dilution are sufficient to use in a patient whose personal equation in this respect is not known, or in whose case the solution may penetrate raw surfaces or highly vascular areas, such as

the gums. The minimum fatal dose is fixed rather doubtfully by McLane Hamilton at half a grain.

Much stronger dilutions may be used to paint upon unbroken surfaces; indeed the drug is not readily absorbed by the skin, though it produces an anæsthetic action upon it. Mucous surfaces must be dealt with more cautiously. This anæsthesia seems to arise in all animals possessed of a nervous system—even in molluscs, crustaceans, and the like—when submitted to the action of coca. The action of the drug does not seem to be cumulative. Rules for the use of cocaine in surgery by Reclus seem to be regarded by those best able to judge as trustworthy and sufficient.

Resorcin, chloretone, or other antiseptic must be added to solutions of cocaine required to be kept. A mixture of cocaine and adrenalin has recently been employed for injection as a local anæsthetic. It is very satisfactory and less prone than cocaine to produce untoward effects. The cocaine, by diffusion into the surrounding parts, can still paralyse the peripheral sensory endings as perfectly as if injected alone; but, on account of the intense vaso-constriction induced by the adrenalin, it is absorbed much more slowly.

Eucaine, an artificial alkaloid, is beginning to take the place of cocaine; it is only about one-fifth as toxic, but its anæsthetic action is more slowly developed, and not so permanent. It does not constrict vessels nor dilate the pupil like cocaine.

Symptoms.—When a relatively excessive dose has been taken the patient becomes pale, faint, and giddy, and breaks into a sweat; he complains of creepings on the skin, palpitation, and a sense of anxiety in the precordial region; the pulse begins to rise rapidly in rate and to fail in strength, and he becomes loquacious, agitated, or even hysterical. The dilated pupils fail to react to light and accommodation; the respiration becomes panting; faintness passes into prostration with more or less loss of consciousness, and perhaps with convulsions; cyanosis deepens, and in grave cases Cheyne-Stokes breathing is said to occur. The muscular system suffers greatly: pains, often sudden and severe, are felt in the limbs, and cramps, unilateral or bilateral, take possession of them, chiefly on the side of the flexors, which may amount to general rigidity and even to well-marked tetanus. Trismus and tetanic seizures are also recorded (Schede). Some anæsthesia of the skin is to be determined from the outset if the patient be able to testify to it; but he may soon fall into a delirium with hallucinations, become violent, suicidal, or even homicidal (Borrmann); on the failure of the sphincters urine and fæces are passed into the bed. Cocaine first excites the central nervous system, especially the motor area, and this stage is followed by depression, during which death may occur from collapse or respiratory failure.

In cocaine poisoning, even in the midst of such grave symptoms as these, we may be more hopeful of recovery than in some other intoxications. The duration of the symptoms is short, whether they end in recovery or in death.

The treatment is such as the symptoms indicate: it consists in the horizontal position, the use of alcohol and diffusible stimulants, such as ammonia, by the mouth, the rectum, and the subcutaneous tissue; the inhalation of oxygen, and, if necessary, artificial respiration. Intravenous injections of two or three ounces of normal saline solution are said to have proved helpful. Nitrite of amyl has been currently recommended when the arterial blood-pressure is much raised. The inhalation of chloroform or ether may be used for convulsive attacks. In case of recovery some nervous disturbance—such as insomnia, vertigo, mental depression, and tingling in the limbs—may continue for some days. If a fatal event ensue, the convulsions, tonic and clonic, will continue and coma will set in, so that the status epilepticus is established. In some respects the symptoms may be likened to those of poisoning by atropine. If the drug had been taken by the mouth the stomach should be emptied.

Morbid Anatomy.—In this there is nothing very characteristic, and unless cocaine be detected in the organs of the body, the cause of death cannot be ascertained by autopsy alone. Ehrlich says that changes are to be found in the hepatic cells—a "vacuolary" degeneration: the cells are large and even enormous in size, the nuclei being atrophied. The liver is much enlarged, and looks pale from fatty change. During life the drug is said to injure and destroy the leucocytes.

Chronic Poisoning. Cocainism.—Sensitive as many persons are to small doses of cocaine and its salts, yet by habit the doses may be enormously increased, as in the case of other like agents. Cocainists have frequently been known to take from thirty to forty grains in a day; but not with impunity: the effects of chronic intoxication by cocaine are even more terrible than those of morphinism. Like morphine and alcohol, and unlike coffee and tobacco, coca brings the consumer into hopeless bondage. It is alleged that the habit is on the increase, that it is taken for its sustaining virtues in physical exercises, and again as a cordial in the "coca wine" so recklessly sold to the public. If there be cocaine in the wine the morals of the buyer suffer, if none those of the seller. Coca snuffs and lozenges are also sold for common use. The habit is said to prevail, chiefly in the form of hypodermic injection, in Paris and in the United States.

Symptoms.—The first effects of the drug, at any rate in those who are habituated to it, consist in a sense of well-being, briskness of perception, and removal of fatigue, which make the drug, like others of its kind, attractive to those who are at once keen for life and yet soon fatigued. Perennial joy and vivacity seem promised to them. The effect, however, is very fleeting, more fleeting than the gifts of morphine, and is bought even at a greater price. For these qualities the drug has been used in the treatment of melancholia; but the relief obtained is transient, and is followed by a depression which more than undoes the momentary good.

So also with those who use cocaine for purposes of intoxication—depression and insomnia soon supervene, and the victim is drawn to the more and more frequent repetition of his doses, and to increase of the

quantities of each. As this fatal bondage is tightened symptoms of chronic intoxication come on. The temporary prostration and nausea grow worse (that is, if the drug be withheld); the appetite fails; diarrhœa may set in; fits of semi-consciousness appear with no subsequent recollection of that which has passed; a persistent tremor invades the muscles, especially of the upper limbs, and the nights are sleepless. As the habit progresses more permanent signs of deterioration shew themselves: the face becomes sallow. the eyes sunken, and the whole body emaciated; the will becomes weakened to the point of imbecility; the voice is enfeebled to whinings and fretful pulings; hallucinations possess the senses; the limbs become cold and tormented, as is the rest of the skin, with sensations as of creeping animals or vermin; the mind gives way, and delusions of persecution are prominent in the wreck of intelligence. If the habit be still continued the abasement becomes profound. Now few persons would fall into this pit were it not that the use of coca has been recommended. most unfortunately in our opinion, by some physicians as a means of escape from morphinism. Were the value of coca in this respect more than it is, so baneful a cure should have our aversion; but, as we believe that it has very little value of this kind, and that indeed the end desired can be better attained in other ways, it is to be hoped that the cocaine habit will soon be forgotten.

The first effect of cocaine injections is on the circulation: the pulse becomes quicker and the peripheral arterioles contract; the contraction is brought about both by excitation of the vasomotor centre in the medulla and of the nerve-endings in the vessels. The result of these actions is that the arterial blood-pressure rises. As the effects of the drug begin to wear off, as excitement gives place to depression, the opposite circulatory conditions to those described obtain and blood-pressure falls. It is a pity that no trustworthy records of blood-pressure in man during cocaine and morphine narcosis have yet been recorded. As the effects pass off a blunted appetite and a renewed insomnia intensify the patient's sufferings. Such a patient left to himself becomes enslaved to both drugs, and must run up the doses to large quantities—to 30 or 40 grains of each. As Erlenmeyer shrewdly says, the cocaine is far less effective in removing the morphine symptoms than is morphine itself; so that it is better to use morphine in the cure than this new and treacherous ally.

Prognosis.—The slavery of coca is worse than that of morphine; it is more destructive of mind and body, and harder to put aside. The morphinist still retains some desire to defeat his enslaver, and is filled with gratitude, at any rate for the time, when the cure is complete. The cocainist, on the other hand, is so reduced in intelligence that he neither desires emancipation nor feels any thrill of joy when released; his brain is so bemused that he cares nothing for freedom. Hence the prognosis in cocainism is worse, even when skilfully handled in a retreat, than in morphinism; the course, if the mind is to be restored, must be much longer, five or six months at least, and the result is less definitely hopeful. This is not true for those cases in which the cocaine habit is superadded

to the morphia habit; in these the cocaine can usually be omitted without great difficulty.

Treatment.—The only possible means of dealing with a cocainist is to place him in a retreat where such cases are treated with sympathy and skill. Chloral or trional are useful aids in combating the sleeplessness and distress; and massage and feeding in repairing the wasted tissues.

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ETHER

The story of ether drinking is admirably told by the late Mr. Ernest Hart in an article published in the *British Medical Journal* of the 18th of October 1890.

We find from Mr. Hart's article that Sir Benjamin Richardson had long been aware of the practice; and that Mr. H. N. Draper had published an account of it in the *Medical Press and Circular* of the 30th of May 1877. Dr. Walter Bernard of Londonderry, whose personal experience extends over forty-two years, says that ether drinking has been known to him during all this period. According to Sir Benjamin Richardson this abuse of ether was introduced into Draperstown, in South Derry, in 1846-47, whence the practice seems to have spread over certain parts of the county of Londonderry, and into the borders of Antrim and Tyrone. Ether drinking was practised also in Lincolnshire, and Mr. Hart had reason to believe that it was by no means unknown in London.

Enormous quantities of "methylated spirit" are consigned to Ireland by large manufacturers, and from this crude spirit the "methylated ether" is obtained, and is sold in drams at the shops. It is to the introduction of this cheap ether, and to the activity of the revenue officers in

hunting down the illicit whisky stills, that the prevalence of ether drinking may be traced. The story that the practice arose in an evasion of "the pledge" against alcohol in the time of Father Mathew, seems to be a "picturesque inaccuracy." As a result of Hart's reports the Government imposed certain restrictions on the sale of ether, which have had the effect of greatly reducing the vice.

The cheapness of the intoxicant seems to promote its use. Its retail price is about 1d. for two drachms, or even a ½d. for a drachm and a half. The Rector of Cookstown reported that "in small poor grocery shops ether is sold without restriction, and it is hawked about in exchange for eggs and farm produce." One of the guards of the Derry Central Railway says that "the smell of ether in the third-class carriages on market-days is disgusting and abominable."

Mr. Draper tells us that the usual quantity of ether taken as a dram is from two to four drachms; and that this dose is repeated twice, thrice, or even four and six times daily. As it is almost insoluble in water, it is usual, except perhaps with the moderate drinkers, to take a mouthful of water first, and after the ether another mouthful of water. An experienced drinker by holding his nose can take a large quantity undiluted. There are tales of persons who would take so much as a pint during the period of an ether debauch. One draught—less than a wineglassful—will produce intoxication in any one unaccustomed to the drug.

The special temptation of ether, as compared with other intoxicants, lies in the transitoriness of the immediate effect; moreover, little or no punishment remains, such as nausea, dry mouth, headache, and the like. Thus, what the late Dr. Norman Kerr called "the drama of intoxication" could be repeated several times a day, and for a small outlay.

Even respectable people take the ether and without shame, pretending that it is useful as a medicine for "the wind in the stomach," and other ailments. It is largely drunk also at wakes and dances. Its effects are very rapidly produced, and the stage of excitement is very marked. "Those under its influence shout, dance, laugh, and act like maniacs: if the dose has been heavy they may fall down writhing and foaming at the mouth. They generally recover soon, and feel low and depressed; and often then will renew the dose, for which they have a strong craving." "A smaller dose is exhilarating, and produces a feeling of lightness as if the person could fly." Profuse salivation often follows the drinking of ether, then rather violent eructations; the face becomes flushed, and, if large quantities are taken, may become livid: pallor, weakness, and burning pain at the epigastrium follow. When the dose is large, frenzy, maniacal excitement, and ultimately stupor supervene. Dr. J. W. Watson (quoted by Hart) says: "The ether drinkers agree that it is a very pleasurable form of intoxication, and others can see that it is a very violent form. But the most violent form is produced when whisky and ether are both taken." Ether drinkers are very quarrelsome in their cups, the intoxication being decidedly of the pugnacious kind.

Pathology.—Of the remote effects of ether little is known. The late

Sir Benjamin Richardson expressed almost regret that no grievous lesions arise in these subjects to point the moral of excess as in alcoholic drunkards. Chronic gastritis and dyspepsia seem to be the chief consequences. Ether drinkers, however, suffer from debility, great nervous prostration, tremors (especially in the neck and forearm), indigestion, irregular action of the heart, subacute gastritis, a peculiar whitish sallow complexion, and, in some cases, a peculiar livid cyanotic face. Dr. Walter Bernard (quoted by Hart) says that there follow wasting both of fat and muscle, enfeebled circulation, pale lemon or brown skin, exaggerated reflexes, and profound degeneration of the moral character. The victims fall into a kind of hysterical state, lose all self-respect, and will lie and steal to procure their favourite stimulant.

There does not seem to be any evidence to prove that ether drinking directly produces insanity; though of course it may favour its occurrence in persons thus disposed.

The habit leads to crime only through the violence and pugnacity so characteristic of this form of intoxication. In discussing the physical consequences, we must remember that these have not yet been thoroughly investigated by pathologists armed with the resources of modern science.

Chloroform, Chloral, Sulphonal, Antifebrin

It is not necessary to enter into details concerning each one of these and other hypnotics or analgesics. They all bring about a loosening of the framework of the higher nervous matter, and thus weaken the will and the intelligence, and slacken the control of the emotions. Judgment becomes uncertain, action capricious, and temper fretful. The muscular system also, in its enfeeblement, weariness, and tremor, shews a like undoing. As with the former agents, here too there is a craving for the habitual drug: without it insomnia distracts the sufferer. It is often wise for a time to use another drug of soporific virtue in place of the old one, in order to shunt the morbid process before arresting it suddenly. But all bad cases of the kind should be treated in some retreat, whether it be the house of a medical man of skill and shrewdness, or a special institution.

Chloroform.—The habit of chloroform inhalation is especially to be dreaded; fatal accidents are not unlikely to occur in its use by the patient, as the annals of too many households can testify. Chloroform readily relieves asthma and other spasmodic affections; and if the medical attendant cannot prevent the use of this drug he must insist that it shall never be self-administered.

Chloral and chloroform differ in this important respect from other narcotics, that no full tolerance of them is established by habit. However persistent the habit may have been, even a moderate dose may suddenly prove fatal. The physician cannot too strongly impress the treacherous property of the drugs upon any patient who resorts to their use.

Delayed Chloroform Poisoning.—It has now been conclusively shewn that after certain cases of prolonged chloroform narcosis, delayed symptoms of poisoning occur. If a rabbit or guinea-pig be anæsthetised with chloroform during a period of two hours, fatty degeneration and necrosis of the liver-cells follow, and in a considerable proportion death ensues, although not till some days after the anæsthesia. Changes of a similar nature have been observed in man. These cases of delayed poisoning may begin any time from twelve hours to four days after complete recovery from a prolonged anæsthesia. Children are especially susceptible, and any condition which lowers the vitality of the tissues appears to act as a disposing cause.

The symptoms generally begin with vomiting, the pulse being very rapid and feeble; not infrequently jaundice is also present as an early sign. The patient becomes excited, delirium follows and passes into rapidly fatal coma: in a few cases the excitement and delirium are absent. The breath has a characteristic sweetish odour, due to acetone, and the urine always contains diacetic acid. Pyrexia is rare, except just before death; albuminuria and casts are found in the urine in a small proportion of the cases. Death generally occurs about the fifth day.

Pathology.—Post-mortem fatty changes have been discovered in the liver, heart, kidneys, and muscles; the kidneys are often affected with a mild degree of inflammation. It is well known that chloroform increases the excretion of sulphates, phosphates, chlorides, and nitrogen in the urine. This condition is not caused by increased oxidation, because the excess of nitrogen is in the form of alloxuric bases such as uric acid, and as ammonia, whilst the sulphur occurs in an unoxidised and complex form, as cystin and related bodies. Associated with these conditions we find acetone, diacetic acid, and β-oxybutyric acid in the blood and urine; a diminished amount of glycogen in the liver and tissues generally; and the appearance of fat in the shrunken cells of the liver and other parts. The augmented nitrogenous elimination appears to be due to an increased acidity of the blood; diacetic, lactic, and oxybutyric acids being apt to appear in any condition of imperfect oxidation. It may be supposed that in the normal metabolism of the proteid molecule a nitrogenous portion is oxidised and excreted in the urine as urea, whilst a non-nitrogenous portion is burnt off as carbonic acid and water: it is this oxidation which is affected in chloroform poisoning. As a consequence there is a deficiency in the formation of carbonic acid; in its place an accumulation of fat appears in the cell, and such incompletely oxidised bodies as acetone and oxybutyric acid are produced.

The problem of how to prevent these deaths is at present unsolved, although we have made a step forward by recognising their cause. It would seem, however, that just as the addition of carbonates to the food prevents the excessive production of acid in the tissues in chloral poisoning, with all its associated evils (Kleine), so the administration of alkalis before chloroform inhalation may prevent these cases of delayed poisoning.

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BEVAN and FAVILL. *Journ. Amer. Med. Ass.* 1905, vol. xlv. pp. 690 and 754. (Contains the clinical literature.)

Chloral.—Chloral presents certain resemblances in action to chloroform. In moderate doses, 10 to 30 grains, it produces a condition identical with natural sleep; in contrast to morphine it has no action on analgesic areas, and the reflexes are not affected. In larger doses, 1 to 2 drs., the patient falls into a deep sleep, from which it is impossible to arouse him completely; both sensibility to pain and the reflexes are now diminished. Respiration is very shallow, because of the direct depressant action of the drug on the medulla; the heart is extremely feeble, and the blood-pressure correspondingly low. Still larger doses produce complete anæsthesia and deep coma. Death from chloral almost always results from respiratory failure, although well-marked and even dangerous cardiac depression is not an uncommon occurrence. Chloral causes metabolic changes like those induced by chloroform; tissue metabolism is increased, although the products are less completely oxidised than under normal conditions, and the gaseous exchanges are diminished. The prolonged use of chloral has led to cachexia, general depression, fatty degenerations, and other conditions resembling chronic poisoning by alcohol. It is mostly excreted, combined with glycuronic acid, as urochloralic acid; this body renders the urine very acid and gives most of the reactions of glucose, but does not permit of fermentation with yeast. A case of chloral poisoning was recorded by Dr. Colenso, in which one ounce of chloral in crystals was swallowed, yet recovery followed. In a somewhat similar case, recorded by Hulke, 5 drs. were taken, and recovery followed after artificial respiration and the administration of hot coffee by the bowel and otherwise.

Treatment of poisoning by chloral should consist first in the evacuation of the stomach by the tube; emetics cannot be relied upon, as the medulla may not be sufficiently active to allow of vomiting. The patient should be wrapped up in warm blankets, and medullary stimulants, such as strychnine or caffeine, administered. Artificial respiration must be kept up when necessary, and inhalation of oxygen may be of assistance. Small and frequently repeated injections of adrenalin may be employed to tide over emergencies. For this purpose one or two minims of the 1 in 1000 solution, diluted with 10 or 20 parts of saline solution, may be put directly into a vein. In cases of emergency, the administration of alkaline carbonates, hypodermically, should form a routine practice.

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Sulphonal is a pure hypnotic and possesses no analgesic properties. Successive doses may give rise to poisonous symptoms from cumulative action, the excretion of the drug being slower than its absorption. The symptoms shew themselves by some confusion of thought and hallucinations, by gastritis and by hæmatoporphyrinuria; this may be associated with a peculiar form of dyspnœa. The cherry-red coloration of the urine is due to an iron-free product formed by the decomposition of hæmoglobin. These phenomena can be avoided, according to Kast, by intermitting the administration. Tyson and Croftan found that the quantity of hæmatoporphyrin passed in one day may reach even a quarter of the total hæmoglobin in the body, and although this amount is exceptional, still very considerable amounts are so lost. Sulphonal is excreted very slowly as ethyl-sulphonic acid.

A considerable number of cases of poisoning by sulphonal are on record. Dr. Wright Hardwicke records the case of a dipsomaniac woman, aged thirty-seven, who, after consuming a variety of strong alcoholic drinks, including turpentine, chewed up some sulphonal tablets to the amount of 265 grains. She was found shortly afterwards in a state of stupor. Five hours later she was seen by Dr. Hardwicke, who found her sleeping on her side with her knees drawn up, and the pupils slightly contracted and insensible to light. When roused she smiled graciously, and lapsed off to sleep again; she tried once to raise herself in bed, when she fell powerlessly back again. Next day the legs were found to be extended, and the soles of the feet were arched in a state of extreme flexion. The bowels were confined. She slept from 5 P.M. on June 1 till 5 A.M. on the 4th—sixty hours; she did not regain speech till the 7th, nor the power of locomotion till the 9th.

The other sulphones, trional and tetronal, may induce similar symptoms to those of sulphonal.

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Antifebrin (Acetanilide).—The so-called antipyretic members of the coal-tar group—antipyrin, phenacetin, lactophenin, exalgin, antifebrin, and a host of others—all possess certain actions in common, but differ considerably in their toxicity. They are all, with the exception of antipyrin, oxidised in the body to para-amido-phenol $\left(C_6H_4 \begin{smallmatrix} \diagup OH \\ \diagdown NH_2 \end{smallmatrix}\right)$, and in proportion as this body is present in the tissues toxic symptoms are produced: antifebrin is the most readily oxidised and is much the most toxic. It is true that in some persons medicinal doses of any of these drugs may produce poisonous symptoms, but larger doses give rise to similar symptoms in all people.

Poisoning by these drugs often begins with catarrh, burning in the

mouth, nausea, and vomiting. The cutaneous vessels are dilated, the skin is covered with a profuse perspiration, and not infrequently rashes resembling those of scarlatina, measles, or urticaria may be seen. The face usually becomes livid from the formation of methæmoglobin, and in the more severe cases blood can be detected in the urine. But methæmoglobin formation is not the only cause of the cyanosis, because cyanosis may occur when no methæmoglobin is present. This condition is accompanied by dyspnœa and acceleration of the pulse, and may last from a few hours to several days. By far the most serious symptoms are attacks of fainting, which on rare occasions have been followed by collapse and death. The fatal cases of collapse which are on record have, with few exceptions, been febrile cases, and the fatal termination cannot be regarded as entirely the result of the depressant action of the drug on the medulla. It is well known that if the body-temperature be suddenly lowered shivering and rigors supervene, from an attempt of the part of the centre to increase the production of heat. Moreover, if the stimulus of fever be suddenly removed there is a greater tendency for the partly exhausted nervous and circulatory systems to fail and so aid in the collapse. Collapse is characterised by very shallow respiration, an almost imperceptible and very rapid pulse, and a subnormal temperature. Para-amido-phenol is excreted in the urine combined with sulphuric or glycuronic acid, and gives the urine a smoky tint, although a like tint may arise from methæmoglobin. The condition of the circulatory system is the chief source of anxiety in these cases of collapse. The splanchnic vessels become enormously dilated, and the great bulk of blood lies stagnant in the circulation.

Treatment should consist in the application of warmth to the surface of the body and the internal administration of circulatory and nervous stimulants. As a circulatory stimulant perhaps tincture of squill is the best, for it raises the blood-pressure and constricts the vessels more than the other members of the digitalis group. To ensure absorption it should be injected deeply into the subcutaneous tissues.

Tobacco

The effects of tobacco, for better or for worse, are so well known that it is not necessary to delay the reader by a long description of them.

Acute poisoning by tobacco can only occur by so strange a mischance that this part of the subject certainly need not be dealt with at length. If tobacco were swallowed in poisonous doses, the stomach-tube must of course be used, and tannin may be administered to neutralise the nicotine. The resulting symptoms must be treated by stimulants, such as subcutaneous injections of ether and the like. The enema of tobacco, once employed in medicine, was apt to be followed by dangerous consequences, and has properly fallen into disuse. "Every schoolboy knows" the deadly pallor, the cold sweat, the horrible nausea, and, if

he go farther, the diarrhœa and collapse which follow the first doses of the drug.

Chronic tobacco poisoning, now that snuff-taking has practically ceased, is met with in smokers only. That tobacco used moderately is generally injurious seems improbable, at any rate the mischief of it is not proved. The consumption of the drug, even in considerable quantities, as he who runs may see, is in many persons compatible with excellent health and with the propagation of sound progeny. Observers who assert the contrary point to town-bred youths, in whom other mischievous factors are at work. Thus used, tobacco is not injurious to most persons, and has its indirect benefits in soothing fatigue and restlessness. It is, however, as true of tobacco as of other agents affecting the nervous system, that the personal equation is to be regarded. The quantity consumed with impunity by one man is poisonous to another; each smoker must estimate his own resistance and regulate his doses accordingly. Vertiginous sensations, tremor, treachery of memory or of utterance, cardiac flutterings, insomnia, should be at once regarded as warnings. If a smoker who is not quite a novice become aware of such symptoms he may be assured that he is not endowed with much tolerance, and must smoke with caution. Probably all persons by persistent effort can establish some measure of tolerance; but the susceptible person remains relatively obnoxious to the drug, and is more likely to suffer from evil consequences than others more hardily constituted in this respect.

Tobacco smoke contains several poisonous bodies, pyridine bases, hydrocyanic acid, collidine, and some higher homologues of nicotine. A recent analysis of cigarette smoke obtained by means of an aspirator gave the following results for 100 grammes of original tobacco consumed: HCN 0·080 per cent, pyridine 0·146 per cent, nicotine 1·165 per cent, NH_3 0·360 per cent, CO 410 cc. The smoke usually contained about 50 per cent of the nicotine originally in the tobacco; but the quantity varied according to the length of the mouth-piece. All the ill-effects of excessive smoking can be explained by the presence of nicotine and pyridine bases.

To understand properly the ill-effects of tobacco in those in whom the use has become habitual, it is necessary in the first place to describe the way in which nicotine acts. This alkaloid first excites and later depresses the sympathetic nerve-cells throughout the body. The circulatory system shews these effects during the stage of stimulation by cardiac slowing (excitation of the intracardiac vagal cells), vaso-constriction, and a considerable rise of blood-pressure. But in the later and more pronounced stage of depression, the heart-beat is quickened by the paralytic action on the intracardiac ganglia and the blood-pressure falls, from vaso-dilatation. In man cigar-smoking produces a distinct though not very considerable rise in arterial pressure. When the smoking ceases the pressure rapidly falls somewhat below the normal. Boveri, by the intravenous injection of a 10 per cent infusion of tobacco

into rabbits, succeeded in producing atheroma of the vessels. There is no difficulty, as we ourselves have shewn, in producing well-marked atheroma in rabbits by the intravenous injection of any drug which considerably augments the blood-pressure. Thus adrenalin, ergot, nicotine, and squill may all induce this condition. In all the conditions mentioned the rise in blood-pressure was transient, never lasting for more than a few minutes, and the arterial degeneration appeared to depend upon sudden and violent vaso-constriction. These conditions do not obtain when tobacco is smoked, and there is no experimental and not much clinical evidence that smoking disposes to atheroma.

The movements of plain muscle throughout the body are first inhibited and later augmented, because of the early stimulation and later depression of the nerve-cells. Peristalsis is slightly increased by removing inhibitory influences, and hence the after-breakfast pipe. On the central nervous system the main action of nicotine is to facilitate the passage of impulses, so that reflexes are increased and sometimes strychnine-like convulsions have been observed. Degeneration of the cells of the anterior cornua have been described by Vas in rabbits dosed with nicotine.

Among the slighter consequences of tobacco are decay of the teeth, giddiness, sleeplessness, muscular tremors, generally of a fine rhythmical kind, and chronic granular pharyngitis. The inflammation of the throat and trachea leads to hoarseness and excessive secretion from the mucous glands, and is no doubt due to the pyridine bases, because the products of dry distillation of almost any leaves will produce the same effect. It is probable, however, that the importance of tobacco smoke in producing diseases of the throat has been grossly exaggerated. In respect of severer consequences there is still some difference of opinion : most people are agreed that with one exception, namely, atrophy of the optic nerve, the degenerative diseases of the central nervous system—such as tabes and the like—formerly attributed to tobacco were but coincidences. Tobacco amaurosis seems to stand alone among mischiefs so grave. For a further description of this affection the reader should consult the article on medical ophthalmology (vol. vi. p. 845).

On the mucous membrane of the mouth and tongue we have very certain evidence that nicotine may produce either a superficial or chronic glossitis, but whether epithelioma of the lip be a direct consequence of tobacco smoking is an open question ; so many persons smoke regularly that it is difficult to apply the method of concomitant variations in this case. It is probable that in a person so disposed, the careless use of a short or hot pipe may favour the manifestation of this evil. In a person not so disposed it seems improbable that the evil would thus be induced.

Of lesser ills vertigo is not a very uncommon sign of excess or of intolerance of tobacco. It may be so severe as to disable the sufferer, or even to throw him into bed. This symptom we have noticed rather in those who smoke cigarettes, perhaps because in this practice the smoke is generally inhaled. It must not be forgotten also that cigarette smokers get through a great deal of tobacco ; twenty cigarettes a day is a common

allowance, and fifty by no means an unknown one. But the symptoms may appear on the use of a pipe or cigar.

Kjellberg has described a peculiar psychological state, in which hallucinations of sight and hearing obtain, and in which the patient passes through psychical waves of exaltation and depression; this condition he states is more likely to be induced by chewing than smoking. After vertigo symptoms referable to the stomach and heart are most frequently found. A grinding pain of a peculiarly disquieting kind may come on fifteen to thirty minutes after food: this pain we believe to be due to hyperacidity, because it is relieved by alkalis, and also by taking food again, as in the dyspepsia of hyperchlorhydria. Flatulence of the stomach is often met with in smokers, but usually in connexion with irregularity of the heart: this flatulence is often met with in other affections of the heart, and it is hard to apportion the causative relation between the two events. Cardiac irregularity is a frequent consequence of tobacco smoking, lagging and intermission being the earlier forms of it. One case is known to us of a man whose general health is excellent, who is by no means a neurotic subject, and whose heart stands work well in all other respects, in whom intermittence of the heart may occur for many days if he remain for an hour or two in a room with many smokers. He dare not sit in a close smoking room or in the smoking compartment of a railway carriage. The intermittence may not begin until the next day, or the next but one, but then comes on with the certainty of a laboratory experiment; it gets worse during the next day or two, and then gradually passes off in a few more days. He never suffers from any cardiac disorder unless exposed to tobacco, but this proclivity has hung about him for many years. He has no dislike to the drug, nor does he feel any immediate discomfort from it. In smokers, even in those who smoke not immoderately, this proclivity is common enough. Prof. Allbutt has described the symptoms in two brothers of about thirty years of age who came to him for life assurance. They were both fine vigorous men of good family stock, and they were naturally much nettled by his declining them. After leaving off tobacco for four or five weeks the intermittence disappeared. Cardiac irregularity under the influence of tobacco is not confined to intermittence; it may go on to utter disorder both in rate and rhythm (delirium cordis). The usual form is for two or three strong or throbbing pulses to be followed by a run of small quick ones; the blood-pressure being low in all. Occasionally in intermittency the stops may have a regular distribution, as, for instance, at every third or fifth interval. "Tobacco hearts" are common enough in young men who smoke freely before becoming thoroughly seasoned. The main feature in these youths is palpitation, the pulse being usually quickened from interference with vagal ganglia. The heart has a laboured and hesitating gait, different from the ordinary "young man's heart" and from the effects of organic disease. The hesitation is usually accompanied by a sense of discomfort referred by the patient to the cardiac region, probably to the heart. In tobacco intermittence the patient is always conscious

of the stop and roll forward, a sensation which in disease of the muscular tissue of the organ is not always but generally absent. The discomfort in the cardiac region is the first symptom to be noticed. In still more advanced cases the quickening and arrhythmia may be extreme, and the condition resemble that of delirium cordis; in these cases sudden syncope may occur.

Insomnia is said to be a consequence of smoking tobacco in certain circumstances. Every smoker knows that a stronger cigar than usual may keep him awake; and it is alleged that the ordinary use of the drug may act thus as an excitant in one whose brain is unusually susceptible, or is in a state of irritability from overwork or anxiety. Usually the effects of tobacco are soothing and favour sleep; yet, like other narcotics, tobacco has its effects of stimulation.

The last group of symptoms of chronic poisoning by tobacco which we shall discuss is the group of neuralgias. These are of some importance, as until the cause is removed the pain may be recurrent and severe, and sometimes the cause is not hit upon. In one smoker we remember the neuralgia was seated in the anterior crural nerve and was acutely lancinating. Happily the suspicion of tobacco was awakened; in abstinence he found perfect relief, and, as a return to tobacco was repeatedly found to recall the pain, he determined to remain abstinent and well. In other cases, and much more commonly, the pain is about the intercostals, and the humeral and scapular regions. Dr. Judson Bury records peripheral neuritis as a rare consequence of the use of tobacco.

A violent and alarming form of this pain is the so-called tobacco angina, described by Peter and many others. There is not much difficulty in distinguishing tobacco angina from the form which depends upon cardio-vascular disease; but the diagnosis is not to be made by the mildness of the pain. The most frightful attack of tobacco angina (if so it is to be called) that we ever saw was in a gentleman then no longer young (about 55 or 60), who informed us that he often smoked as many as twenty cigars a day. While in the consulting room he fell into a fit of the "angina," which was so severe as to make him writhe off his seat and over the edge of a couch to the floor. He pressed his hand to his heart, groaning piteously, if that could be piteous which witnessed in his favour. No man in an attack of true angina writhes or groans aloud; nor does a true attack last long enough for manœuvres of this kind. The note of angina pectoris is terror-stricken stillness; the patient dare not even breathe, lest he die in the act. Moreover, except in the rare "chronic" form of angina pectoris, the attack does not last so long as in the tobacco form; and in chronic angina there is rather a persistent series of attacks than one attack of long duration. Yet the tobacco seizure likewise may sometimes be startling in its suddenness, and in its likeness to angina pectoris. Tobacco angina must, however, be regarded as extremely rare, since Professor Osler's experience in 1897 was limited in two cases which he regarded as belonging to the toxic or vasomotoral group of anginas. Post-mortem examinations in these cases are neces-

sarily very rare and very ambiguous, but besides arteriosclerosis Fararger has described fatty heart in a patient who had killed himself by excessive smoking.

Tobacco, in common with most kinds of chronic poisoning, tends to anæmia; this character should put a smoker on his guard. It is useless to go into the treatment of chronic poisoning by tobacco; there is but one means of cure, namely, to stop the practice of using it in any form. In our opinion he who habitually poisons the structures of his heart is on the way to dilate it, or to produce other statical deterioration of the organ. The way may be a long one, but we have seen many pilgrims far advanced upon it. Even if the patient submit frankly to give up tobacco his heart may long remain irregular; we have reason to suspect that in some cases occurring late in life perfect rhythm is never recovered.

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Tea and Coffee

It is a remarkable and at present unexplained fact that almost all nations, uncivilised as well as civilised, should have chosen as national beverages infusions or extracts of plants containing one or more alkaloids related to xanthine. It is the more remarkable as these bodies possess neither characteristic taste nor odour to guide to the selection of the plants in which they exist. Coffee from Arabia and tea from China both contain caffeine: cocoa which comes from central and South America contains theobromine or dimethyl-xanthine,—caffeine being trimethyl-xanthine. From central Africa we get the kola nut containing caffeine and a little theobromine; from Brazil, Guarana paste, which also contains caffeine and theobromine; and from the Argentine Republic, Paraguay tea, which contains a little caffeine.

It were an idle thing to write at large upon these articles of common consumption; every housewife may claim to know as much of their virtues as the physician. A few points seem, however, to be worth discussion.

Tea and coffee are nervine stimulants without narcotism. It would seem that in their case the work of the nervous matter is increased directly, not let loose by narcotism of controlling centres, as seems to be the case with some of the drugs previously described. Caffeine exerts its action mainly upon the higher centres in the brain, on those parts connected with psychical functions. It seems to act by facilitating the

perception of sensory stimuli and the association of ideas. Mental activity is increased, the interpretation of sensory impressions is more perfect and precise, and thought is rendered clearer and quicker than in the normal state. Caffeine also facilitates the performance of physical work. Experiments have been conducted on soldiers who were required to march a fixed distance with all their kit; and it was found that they could perform more work with less fatigue when marching on some beverage containing caffeine than on beef-tea or alcohol. This stimulation may, as is usual in such cases, be followed by exhaustion; according to the degree of the previous stimulation. When taken in moderation, however, this reaction seems either not to be felt, or to be so slight as not to be noticed; in ordinary use the stimulant seems to be clear gain. In not a few persons, however, evil consequences are manifest enough. Another interesting point of distinction is that tea and coffee, unlike tobacco, get no strong hold upon the users of them. A very few persons may find a difficulty in breaking their favourite habit, but even these would be ashamed to admit that they could not do so if necessary.

As also in the case of tobacco, the tolerance of individuals differs very widely. Some persons will and do drink strong tea or coffee for breakfast, luncheon, at five o'clock, and again after dinner; and, so far as one can tell, with impunity. Others cannot touch tea even once a day without disagreeable consequences, such as malaise, restlessness, excitement of mind, followed by confusion and depression; and so forth. Coffee makes itself felt as an evil more readily than tea, perhaps because it is taken in a stronger infusion or decoction, or is absorbed more readily.

The active principle, common to tea and coffee, is probably the main cause of the insomnia which is due to the use of these articles. But caffeine cannot be the only cause, or even the chief cause, of the other ill effects which follow the abuse of these beverages, because these do not all follow the use of caffeine in its pure state; nor are the symptom-groups in tea and coffee poisoning identical, as they ought to be if the poisonous principles in the two be identical. Coffee contains less than 1 per cent caffeine, which is all extracted when making the beverage, so that an average cup of coffee contains from 1 to 3 grains of caffeine. Volatile substances are also present which have the effects of the essential oils: it is probably by the presence of such bodies that the after-dinner coffee promotes the feeling of comfort and well-being. Coffee, also probably on account of its volatile oil, augments peristalsis; caffeine has no such effect.

We have seen several well-marked cases of coffee excess, and its symptoms are not without character. The sufferer is tremulous, and loses his self-command; he is subject to fits of agitation and depression; he loses colour and has a haggard appearance. The appetite falls off, and symptoms of gastric catarrh may be manifested. The heart also suffers; it palpitates, or it intermits. As with other such agents a renewed dose of the poison gives temporary relief, but at the cost of

future misery. Such persons, when assured that the cause of their troubles is coffee, will abandon the use of it without much unwillingness, in which case they are restored to health in a short time. In Watson's language, by renouncing coffee they may get rid of their palpitation and of their apprehensions together. Neither tea nor coffee causes palsy.

The effect of caffeine on the circulatory system is often misunderstood. On the heart its most characteristic action is acceleration, the force of contraction being only slightly affected. In larger doses the rate of the beat is still further quickened by exaggerating the irritability of that portion of the heart-muscle (excito-motor area) which gives the rhythm to the heart: as the acceleration increases the muscle no longer has time to relax properly during diastole, and ultimately the heart enters into delirium cordis. But caffeine also stimulates the medulla, and for a time during the early stages of caffeine poisoning the vagal centre holds the heart-beat in check; and so we find cardiac irritability and irregularity, intermittence and palpitation. In the early stages of poisoning the stimulation of the medulla causes vaso-constriction and a rise in the general systemic blood-pressure. But caffeine has also a very profound action on the vessels directly, which it tends to dilate, and the battle for the blood-vessels which is continually going on results first in a victory for the centre with vaso-constriction and a rise in pressure; but later, particularly when the central action is wearing off, the peripheral effect becomes the more pronounced, and decided vaso-dilatation ensues with some fall in the pressure.

Tea contains from 2 to 4 per cent caffeine; but, as compared with coffee, much less is taken up in preparing the beverage, the alkaloid being not so readily extracted. Hence an ordinary cup of tea contains much the same amount of caffeine as an ordinary cup of coffee. Tea contains about 7 per cent tannin, and although a good cup should contain little of the astringent, yet it is probable that sufficient may be present to delay the absorption of the caffeine. Tea likewise affects the heart, but not so promptly and directly as coffee; tea seems rather to affect the stomach. Many obscure cases of gastralgia are due to tea, as also dyspepsia of the so-called atonic kind. Besides the sleeplessness caused by either drug, tea has appeared to us to be especially efficient in producing nightmare with groanings, startings, and even hallucinations which may be alarming in their intensity. Another peculiar quality of tea is to produce a strange and extreme degree of physical depression. An hour or two after breakfast, at which tea has been taken, at a time when the energies of the system should be at their best, a grievous sinking, referred chiefly to the epigastrium, may seize upon the sufferer, so that even to speak is an effort; the blood seems to leave the lips, and the speech may become weak and vague. Or gastralgia and palpitation, if the malady take that form, may be so acute as to disable the sufferer for a while. Confusion and giddiness may add to his troubles. By miseries such as these the best years of life may be spoilt, unless the sufferer find his way to a physician who recognises the cause, and by removal of it

sets the patient free. The astringent matters contained in the infusion of tea promote constipation. The anæmia often seen in such cases is in part indirect, and due to the substitution of tea or coffee for good food. Acne rosacea is said by some writers to arise under the influence of tea and coffee; however this may be, it is wise to substitute cocoa in cases of this affection. In out-patient practice in the northern hospitals of England, very obstinate cases of atonic dyspepsia, with sallowness, loss of flesh and low spirits, occur in men in whom no such ailments would be expected. In our experience this malady has shewn itself especially in miners and engine-drivers. The state is a grave one, and leads gradually to the loss of working power, so that at fifty years of age such a patient may become both useless and miserable. This state is largely attributable to the use of tea by the canful; the tea is by no means weak, and too often it takes the place of nourishing food. Unhappily the mischief has often gone too far before the cause is found out and removed.

T. Clifford Allbutt.
W. E. Dixon.

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METALLIC AND SOME OTHER FORMS OF POISONING: INCLUDING POISONOUS TRADES

By Thomas Oliver, M.D., F.R.C.P.

Phosphorus.—Until within the last three years suicidal poisoning by phosphorus had been increasing in this country. During the ten years ended 1903 there were 152 deaths in England and Wales caused by phosphorus, 72 of which were the result of accidental and industrial phosphorus poisoning and 80 of suicide. Included in the accidental and industrial cases of phosphorus poisoning are the deaths of several children. Of the deaths by suicide 20 were males and 60 females. By dividing the decennium into halves we find that between 1894 and 1898 inclusive 79 deaths were caused by phosphorus, of which 35 or 43·3 per cent were suicidal, while for the five years ended 1903, although there were fewer deaths, viz. 75, of these 45 or 62·6 per cent were suicidal. The ease and cheapness with which people can procure phosphorus from lucifer matches partly explain why this poison is resorted to by the poorer classes for suicidal purposes. It is gratifying, on the other hand, to observe that the number of cases of accidental and

industrial phosphorus poisoning fell from 44 for the five years ended 1898 to 28 for a similar period ended 1903—a circumstance which is largely due to Home Office regulations and to the substitution of the comparatively speaking innocuous sesquisulphide of phosphorus for the dangerous white in the manufacture of lucifer matches. The more general use of this substance for heading matches will be followed by a reduction in the number of cases of suicidal poisoning. As a further indication of the trend of the times it may be mentioned that at an International Congress of delegates of most of the European governments held in Berne, May 1905, the total prohibition of white phosphorus in the manufacture of lucifer matches was recommended. There is a varying amount of phosphorus in matches. Roughly speaking, one pound of phosphorus will head 1,000,000 matches. In 100 match-heads Mayet found 55 mgrms. of phosphorus; and Gonning found, in English matches, 32 to 34 mgrms., in Belgian 38. In Münzer's cases each match contained 0·5 mgrm. of pure phosphorus, so that 100 matches would readily cause death, for 7·5 mgrms. (0·116 grain) have proved a fatal dose. Many of the vermin pastes sold in the shops contain as much as from 1 to 2 per cent of phosphorus, and these are always within easy reach of the public.[1]

Commercial phosphorus is obtained from calcined bones by removing the lime with sulphuric acid and deoxidising the residuum with charcoal. It occurs in the form of waxy semi-transparent sticks, which are usually preserved under water. It gives off a peculiar alliaceous odour and takes fire at 100° F. Though usually spoken of as insoluble in water it has been experimentally proved that water dissolves a small quantity of it, that bile has a stronger solvent influence upon it, and that the solubility of phosphorus in each increases with elevation of temperature. It is soluble in bisulphide of carbon, oils, and chloroform. Phosphorus exists in several allotropic forms, of which the red or amorphous is the most common. This form does not take fire at the ordinary temperature, and it is non-poisonous; hence the Swedish matches made with it are harmless. Phosphorus unites with hydrogen to form phosphine or phosphuretted hydrogen—a very dangerous gas.

It is the "white," or, as it is sometimes called, the "yellow" phosphorus which is the principal cause of phosphorus poisoning. The trichloride of phosphorus is employed in some industries, but in very small quantities. In the chemical laboratory this substance has been the cause of poisoning. Butjagin exposed animals to an atmosphere

[1] In Newcastle-upon-Tyne the number of cases of phosphorus poisoning has been large. In the ten years ended 1894, 50 cases were admitted into the Infirmary, 13 males and 37 females. Of these 50 cases 5 died, 2 males and 3 females. The ages of the patients varied from 9 to 74 years, and with the exception of a child 9 years of age, to whom the poison was administered by the mother, she herself having taken it, the cases were suicidal. For the ten years ended 1904 there were 34 patients admitted suffering from phosphorus poisoning, practically speaking all suicidal, 11 males and 23 females, of whom 1 male died and 5 females. So far as the reasons assigned for the suicide are concerned, it appears to me that in the case of men the principal causes are drink and poverty, and in women crossed love or jealousy, poverty, drink, and ill-usage by their husbands.

containing 0·01 phosphorus trichloride per litre of air, and at the end of one hour the animals suffered from rhinitis, conjunctivitis, profuse salivation, abundant bronchorrhœa, and intense dyspnœa. Lewin has produced poisoning in animals by giving them saturated phosphorus water. Phosphoretted hydrogen is a dangerous compound. Acetylene gas obtained from the American carbide of calcium contains 0·6 phosphoretted hydrogen per 1000, while that evolved from Swiss and French carbide contains 0·3 per 1000. Jokote allowed animals to breathe phosphoretted hydrogen in the proportion of 0·01 to 0·6 per 1000. With 0·01 per 1000 the symptoms of intoxication were slight, but with 0·02 there were vomiting and dyspnœa, followed by death in 1½ to 4 hours.

Phosphorus poisoning may be *acute* or *chronic*. The latter form, known as *phosphorism*, is met with in those engaged in the manufacture of matches. Phosphorus, because it is an important constituent of nervous tissue, is administered medicinally in very minute doses, but in these doses its physiological action is different from that of larger quantities. In minute doses it probably acts as a stimulant, improving the nutrition of the tissues, osseous and nervous. Wegner has shown that when adult animals receive small doses of phosphorus the spongy tissue of the bones becomes thickened and the compact portions more dense. New osseous tissue is subsequently developed upon the inside of the shafts of the long bones, in some instances even to the obliteration of the marrow cavity. Therapeutically it is believed that the drug enters the system as phosphorus, and not as phosphoric acid ; the proof of this is that in cases of poisoning, not only does the breath smell of phosphorus, but the blood is found to contain it. While phosphorus may, yet it does not always, act as a poison by becoming changed into phosphoric acid in the body, for the quantity of this acid formed from a lethal dose of phosphorus is too small ; nor can we say that it is by its conversion into phosphoretted hydrogen, as some maintain. We do not know exactly what happens when phosphorus is absorbed into the blood. If it be oxidised it must undergo this change very slowly, for if fresh arterial blood be taken, phosphorus added to it, and the vessel hermetically sealed, the bright arterial colour is not lost earlier than in a control experiment. Lecorché is in favour of the view that phosphorus acts by becoming converted into phosphoretted hydrogen, for there is a close resemblance between the symptoms caused by phosphoretted hydrogen and by phosphorus. According to Lecorché poisoning by phosphorus is the result of two factors—(*a*) phosphoretted hydrogen and (*b*) phosphoric acid. The patient dies, slowly asphyxiated owing to phosphoric acid having destroyed his blood-corpuscles and the phosphoretted hydrogen having deprived the corpuscles of oxygen. At the temperature of the body phosphorus passes into a state of vapour. Bamberger has demonstrated that in this form it readily passes through animal membrane into defibrinated blood ; hence, should phosphorus be present in the alimentary canal, the blood circulating in the walls of the intestine would soon become surcharged with the vapour of it.

Morbid Anatomy.—The cases must be few in which no lesion is found after death; the character of the morbid changes depends upon the rapidity of the poisoning and the manner in which phosphorus entered the system. Usually there are numerous ecchymoses on the skin, on the serous and mucous membranes, and in the muscles and adipose tissue. In a case seen by myself there were numerous small hæmorrhages under the visceral layer of the pericardium. The blood is liquid and dark. If death occur in the early stage there may be a distinct smell of phosphorus. The skin is jaundiced. There is inflammatory redness of the stomach, with swelling or hæmorrhagic erosion of the intestinal mucous membrane. The liver is increased in size in the early stages; diminished if the illness be protracted; it is of a uniform citron or greenish-yellow colour, or it exhibits irregular yellow patches; on section it is bloodless. The gall-bladder may be full or empty. The kidneys are large and their cortex pale, but the medullary portions are congested. The spleen is not enlarged. Microscopical examination shews very marked fatty degeneration of the liver-cells and of the renal epithelia. The muscle-fibres of the heart have lost their transverse striation and contain numerous fat droplets—a change also observed in the voluntary muscles. Beyond an occasional hæmorrhagic point or two, from increased permeability of the capillary walls, and vacuolation of the cells and nuclei in the cerebral cortex, there is nothing to be detected in the nervous system. Lilienfeld and Monti describe a micro-chemical method for detecting phosphorus, which consists in placing sections of the fresh organ in a strong solution of ammonium molybdate, and transferring them in half an hour to a 20 per cent solution of pyrogallic acid dissolved in ether. After remaining for a few minutes they are passed through spirit to oil of cloves, and then mounted in Canada balsam. A yellow or brown colour, best marked in the nuclei, indicates the presence of phosphorus. Overlach found in acute phosphorus poisoning of unimpregnated animals, that certain well-defined changes occurred in the uterine mucous membrane closely akin to those met with at normal menstruation: there was a development of large cells, resembling the so-called "decidual cells" of pregnancy, from the interglandular connective tissue. Apropos of the formation of this decidual tissue in the uterine mucous membrane, Hitschmann and Lindenthal have examined the uterus in nine women dead from acute or chronic phosphorus poisoning, none of whom had been recently pregnant. These observers only found heaps of cells of the flattened cubical type instead of the ordinary cylindrical variety usually met with in the uterine glands. For a discussion of the pathology of the fatty change in the liver, kidney, and other organs found as a sequel of phosphorus poisoning, the reader is referred to vol. i. p. 574.

Experimental Phosphorus Poisoning.—The experiments by Oddo and Olmer confirm what we have learned by clinical experience, viz. that in phosphorus poisoning death may occur within 24 hours without any trace of fatty change being found. Roger and Josué describe two

kinds of lesions present in the bone-marrow of rabbits poisoned by phosphorus: (1) changes such as are met with in infectious diseases and characterised by cellular proliferation, (2) special lesions, and therefore different to those observed in anything else. Subcutaneous injections of phosphorated oil were made into rabbits. The animals lived from 1-7 days afterwards. On microscopical examination of the bone-marrow there were signs of intense congestion, a marked diminution of fat, and a proliferation of large mononuclear leucocytes and giant-cells. The nuclei of these cells had undergone changes. By means of reagents it was impossible to distinguish the chromatin network and nuclear membrane, the chromatin being diffused through the protoplasm.

Symptoms.—The severity of the symptoms and the rapidity with which they appear depend upon the fine state of division in which the poison enters the body. Usually the symptoms appear within one to six hours after swallowing the drug; but if a large piece of phosphorus has been taken they may not arise, for single lumps have been known to traverse the whole length of a dog's intestine without destroying life. In the operation of some poisons there is a marked difference between the symptoms exhibited by animals and by man; but so far as the effect of phosphorus is concerned the symptoms in both are remarkably uniform. On the development of the symptoms the condition of the stomach at the time has an important bearing. The presence therein of milk or fat, which readily dissolves phosphorus, causes an early appearance of symptoms. The poison need not be taken internally. Dr. L. Hill reports the case of a girl who, wishing to give a "dark séance" to her fellow-servants, rubbed some phosphorus paste upon her hands and face. The characteristic illumination followed, but the girl died, with the ordinary symptoms of poisoning, on the eighth day.

Phosphorus poisoning has been known to follow the ingestion of the flesh of an animal that had partaken of phosphorus. Baumel reports the case of a girl who had consumed part of a chicken accidentally poisoned by grains of wheat that had been boiled with lucifer matches and meant for rats, a ruse frequently adopted by the French peasantry to destroy vermin. For a few days after eating the chicken there were no symptoms, but on the fourth day general convulsions came on, followed by colic, burning pain in the abdomen referred to the umbilicus and iliac fossæ, and increased on pressure, slight jaundice, and frequent micturition, the urine being normal. Subsequently she lost the power of walking, the convulsions were repeated, and the inguinal glands became enlarged. There was in this case an absence of the stomach symptoms usually found when phosphorus has been swallowed, but although the phosphorus ingested through the fowl had lost its causticity, it had not parted with its toxicity. The girl ultimately recovered.

Tardieu divides phosphorus poisoning into three forms—(i.) the common form; (ii.) the nervous; (iii.) the hæmorrhagic. In the first form, irritant, nervous, and hæmorrhagic symptoms are blended together; in the second the symptoms are specially referable to the brain and

spinal cord, and, as the name implies, hæmorrhages are characteristic of the third.

During the act of swallowing the poison a disagreeable taste and smell are perceived, and are followed shortly afterwards by pain in the gullet and stomach, and by retching and vomiting. The tongue and throat may become red, dry, and swollen. In other cases a few hours intervene, during which the patient may move about discharging the ordinary duties of life; then vomiting and nausea come on, accompanied by abdominal pain; the breath becomes phosphorescent, and the vomited matter, which consists of mucus tinged with blood and bile, may be luminous in the dark and smell strongly of the poison. For two or three days the vomiting continues, accompanied by gastralgia, perhaps by diarrhœa, and by sleeplessness; the patient meanwhile is utterly wretched. The pulse at this stage may be normal, or feeble and slightly quickened; while the temperature may be normal, or slightly subnormal. By the third day the vomiting usually ceases and the abdominal pain disappears; but this abatement is frequently but temporary, for shortly afterwards—in from 70 to 80 per cent of the cases —jaundice appears on the third to the fifth day, accompanied by coffee-ground vomit and by abdominal pain referable to the epigastrium. The pulse-rate may now fall; but if the case is going to take an unfavourable course it may increase in frequency, reaching as high as 150. The temperature varies: a high temperature is generally regarded as a precursor of death; but in some cases observed by myself the temperature before death reached only to 96° F. In the vomit numerous reddish-brown flocculent masses can be seen; and, on microscopical examination, numerous fat-globules, broken-down blood-cells, and débris are observed. The vomit gives a blue colour with peroxide of hydrogen and tinct. guaiaci, indicating the presence of blood. Once jaundice supervenes, the patient can no longer be regarded as simply under the influence of phosphorus, but as suffering from the consequences of the profound structural changes in the liver induced by the action of this substance upon the hepatic cells. The viscus, at this stage, may be somewhat enlarged and tender; but if the patient survive, the liver rapidly becomes smaller, so much so as to suggest, in the absence of a history of phosphorus poisoning, the diagnosis of acute yellow atrophy of that organ. The urine may be scanty, usually it is about the average in quantity; it may be albuminous and loaded with biliary colouring matter: it frequently contains crystals of leucin and tyrosin. The headache and sleeplessness complained of in the first few days may now be replaced by delirious excitement and convulsions: these gradually give way to coma, preceded by a marked fall of the temperature. Occasionally, in the early stage, when the vomiting abates there is a remission of the symptoms; and it seems as if the patient would recover, but in due course jaundice supervenes. When recovery takes place the amount of poison swallowed has been small, a successful line of treatment has been adopted early, or the phosphorus has become

oxidised in the intestinal canal. When the poisoning is fatal, death may not come for several days; but in the case of children it may happen within the first twenty-four hours, so that the stage during which jaundice usually occurs may never be reached.

In Tardieu's second form of phosphorus poisoning the symptoms are referable from the outset to the nervous system. Not only are there vomiting and abdominal pain, but peculiar sensations in the limbs also, followed by cramp-like pains or paralysis, and by delirium and convulsions with or without jaundice. Gallavardin quotes the case of a match-maker in Sweden who, after inhaling the vapour of phosphorus consequent upon an explosion in the works, suffered from gradual paralysis of the limbs with trembling of legs, arms and hands, and paralysis of the tongue, causing embarrassment of speech. Henschen also found paralysis in a match-maker. Chaumier describes a case of paralysis consequent upon taking a mixture which contained phosphorus, ether, and creasote. In one of Lovot's patients multiple neuritis came on six weeks after taking phosphate of creasote. It is possible that there may have been a trace of arsenic in the compound. Although phosphorus paralysis occurs in animals, we are not so familiar with it in man. Danillo found structural changes in the spinal cord of dogs, a central myelitis with extravasation and pigmentation. Goll and Burdach's columns have frequently shewn signs of degeneration. Chaumier treated an old man of 70 who, a few days after swallowing phosphorus, complained of pain in the feet and knees. This was followed by paralysis of the feet and legs, which lasted for nine months. The knee-jerks were lost. In this patient the symptoms were due either to peripheral neuritis or myelitis, the pain in the limbs and the loss of the knee-jerks being in favour of neuritis. It is interesting to note that the paralysis did not develop until some considerable time after the phosphorus had been taken.

The skin, in addition to being icteric, may become the seat of erythema or of small hæmorrhages; blood may ooze from the intestinal mucous membrane or from the kidney. Jaundice may occur at any time after the first day. The rapidity of its manifestation is a measure of the danger to life; the liver becomes enlarged and tender at the same time, the enlargement being generally uniform. Ingravescent jaundice gives rise to a series of nervous symptoms (delirium, coma, and convulsions) akin to cholæmic intoxication, and is followed by rapid death. On the other hand, the jaundice may gradually disappear, the appetite return, the abdominal pains cease, and recovery, in a few weeks, be fairly complete.

Opinions differ as to the state of the blood, probably because they have been founded too much upon experimental data. Alkaline during life, the blood is generally acid after death. On microscopical examination the red and white blood-cells are normal. Münzer believes that the red blood-cells are increased in number as a primary result, though the secondary effect of the continued use of phosphorus is to cause a diminution. The blood is frequently dark, and not so liable to coagulate as in health. This may be due to destruction of the coagulating ferment.

The urine is almost invariably affected in phosphorus poisoning. In the early stage it may contain a trace of albumin; but when jaundice arises it contains in addition bile-pigments and urobilin or reduced bilirubin. Sugar is generally absent. Hyaline tube-casts may be observed, with or without fat-droplets or fatty crystals; or tube-casts composed of fatty renal epithelia mostly stained with bile, and sometimes mixed with the débris of broken-down red blood-cells. When tyrosin is present it indicates that important changes have already taken place in the liver—that it is the seat of fatty change, and is beginning to atrophy. Hæmatoidin crystals, as well as certain acids—for example, sarcolactic—have been found in the urine by Münzer. During the stage in which jaundice is present the urine is not necessarily decreased in quantity, but its specific gravity is raised and its reaction is acid. A transitory peptonuria may occur. Von Jaksch states that in the earliest days of phosphorus poisoning there is a fall in the total nitrogen eliminated, and that this is followed by a rise. As early as the third day I have observed a very decided diminution in the daily discharge of urea; and this may continue for several weeks in patients who ultimately recover, without any reduction in the amount of urine passed. In fatal cases there is a rapidly progressive fall in the urea, and this becomes well marked the day before death. Some authors maintain that the quantity of uric acid in the urine is slightly increased throughout the illness, also the ammonia. Münzer is of the opinion that the excessive ammonia plays a useful part in the organism by neutralising the abnormal acid products formed by the action of phosphorus upon the tissues. The amount of phosphoric acid in the urine is increased during the early period of the poisoning, but in unfavourable cases it subsequently sinks below the normal; the same holds good as regards the sulphuric acid. When the jaundiced urine from a case of phosphorus poisoning is kept for a time it emits a strong garlicky odour which is increased on adding nitric acid.

When jaundice appears the fæces become pale and contain fatty matter and crystals; they may contain phosphorus and emit its characteristic odour.

Women, if pregnant, usually miscarry after taking a fatal dose of phosphorus. A woman under my observation, who was eight months pregnant, miscarried on the third day; the child was still-born. Labour in these circumstances pursues the usual course; but within two or three days afterwards jaundice appears and gradually deepens in tint; the liver becomes more tender; somnolence increases, and the patient gradually dies comatose. Phosphorus frequently produces a bloody discharge from the uterus. In the dead fœtuses expelled by rabbits that have been experimentally poisoned structural changes are met with similar to those observed in the mother. The mortality-rate is high amongst the children of parents engaged in the manufacture of matches and tainted with phosphorism.

Forty per cent of cases of acute phosphorus poisoning die. It is no

uncommon thing for apparently slight cases to change for the worse; and even after the jaundice has disappeared and the symptoms generally have improved, sudden death may occur by failure of the heart from fatty change. A tardy development of jaundice is a favourable indication, particularly if it be slight and unaccompanied by enlargement of the liver. The retention of the appetite is a favourable prognostic indication. On the other hand, an early appearance of jaundice, and of such nervous symptoms as convulsions and coma, a rapid, small and irregular pulse, considerable enlargement of the liver, hæmorrhages, and an increased temperature, betoken an unfavourable termination.

The diagnosis of phosphorus poisoning is only certain when in the vomited matter or fæces phosphorus is found. The illness may be mistaken for—(*a*) Acute yellow atrophy of the liver; (*b*) Rapidly developing hypertrophic cirrhosis ending fatally by cholæmia; (*c*) Certain forms of sepsis; (*d*) Certain forms of eclampsia; (*e*) Weil's disease; (*f*) Hæmorrhagic small-pox; (*g*) Obscure forms of alcoholic and uræmic intoxication.

In *acute yellow atrophy of the liver* there is a greater tendency to brain disturbance, and also to enlargement of the spleen, than in phosphorus poisoning. The liver, too, decreases rapidly in size, the jaundice meanwhile deepening; whereas in phosphorus poisoning the jaundice appears with enlargement of the liver and runs parallel with it, although in a certain number of cases this organ subsequently shrinks, when the two diseases have a greater resemblance. On the other hand, some writers maintain that it is impossible to distinguish between the jaundiced condition due to phosphorus poisoning and that observed in acute yellow atrophy of the liver. The late Dr. Vivian Poore was of this opinion. The view that in poisoning by phosphorus it is the periphery of the hepatic lobule that is first attacked, and in acute atrophy the centre, is of no pathological value, especially if putrefaction of the body has set in, neither is the presence of leucin crystals in the hepatic cells of any value, nor steatosis of the liver, for microbic saprophytes passing into the liver during life can give rise to a fatty change exactly similar to that caused by phosphorus. The history of the case is of importance. A differential diagnosis can only be made with certainty when phosphorus has been found in the body of the cadaver.

Occasionally *hypertrophic cirrhosis* of the liver appears rather quickly, and leads to rapid death by cholæmia. Upon one differential symptom between this disease and phosphorus poisoning von Jaksch lays considerable stress; namely, the regularity with which during the last few days of life in hypertrophic cirrhosis vomiting of brown sanguineous material occurs; but in my opinion this is not a trustworthy guide. Cases of *puerperal eclampsia* with an icteric tinge might be mistaken for phosphorus poisoning; but in these the temperature, although irregular compared to the transitory pyrexia of the other illness, is generally high and persistent. Besides, the liver is usually not enlarged. Dropsy if present would be an aid to the diagnosis. The amount of

albumin in the urine and the tendency for it to contain blood are greater in eclampsia.

Certain forms of *alcoholic* and *uræmic intoxication* resemble phosphorus poisoning, and are with difficulty distinguished. In all doubtful cases the vomit should be carefully examined. In *hæmorrhagic small-pox* the persistently high temperature would be a guide. In *Weil's disease* the symptoms begin suddenly, usually with a slight rigor; the pyrexia, which is higher than in phosphorus poisoning, lasts for eight or ten days accompanied by headache; and we find also gastric disturbance, jaundice, pains in the calves, enlargement of liver and the spleen, nephritis and erythema—a group of symptoms closely resembling those met with in phosphorus poisoning. The prognosis of Weil's disease is favourable. The proof of poisoning, on the other hand, rests upon the detection of phosphorus in the vomit, in the rinsings of the stomach, and in the fæces; and there are several methods by which this may be accomplished. In Mitscherlich's process for the detection of phosphorus the vomit is distilled with sulphuric acid in the dark. The retort is connected with a glass condenser, and if phosphorus be present luminous rings appear at the point where the fumes come into contact with the cold water. In the method known as Scherer's the vomit is enclosed in a flask with an air-tight stopper; and two test-papers are placed therein, one saturated with nitrate of silver and the other with acetate of lead: should phosphorus be present, the silver paper is blackened whilst the other remains unchanged. Binda and Stoenesco's method consists in the detection of phosphorescence by means of the naked eye, and subsequently in a microscopical examination of the phosphorus. The suspected liquid from the gastro-intestinal canal is taken into a dark room. A few drops of the liquid are allowed to fall into a test-tube. When the upper part of this is heated phosphorescent clouds are seen to rise from the bottom of the tube. A drop or two of the same material is placed on a glass slide, gently heated, and examined microscopically, when little bluish globules surrounded by a thick fog are observed, whose centre becomes whitish-yellow on altering the focus. To the same slide a drop or two of a weak solution of silver nitrate or of ammonium molybdate is added, when the little globules that appeared to be phosphorus gradually become black, while any others present remain of a grey colour. In the urine from a case of phosphorus poisoning leucin and tyrosin may be found—the former as little round or oval spheres not unlike droplets of fat, and the latter as heaps of delicate needle-like crystals. The best chemical test for tyrosin is to dissolve the sediment in hot water, and to add a drop of a solution of mercurous and mercuric nitrate (Millon's reagent), when if tyrosin be present in minute quantity a rose colour at once appears, and a crimson precipitate if there be more than a trace. For a good method of separating leucin and tyrosin the reader is referred to Mr. Wynter Blyth's work.

Treatment.—As the main object is to prevent absorption of the poison, emetics and purgatives must be given at once: for when

absorption has taken place it is difficult to control the consequent organic changes. If the case is seen early an emetic of sulphate of copper should be given, and the stomach persistently washed out until there is no longer any smell of phosphorus. Objections have been raised to the employment of copper sulphate on the ground that it causes gastro-enteritis; but there is little chance of this occurrence if it be given in from 3 to 5-grain doses, freely diluted, every few minutes. Black phosphide of copper is thus formed, which is harmless and readily eliminated by the kidneys. The washing out of the stomach may be accomplished with warm water containing copper sulphate, and subsequently with calcined magnesia. This line of treatment may suffice alone; but for the next few days it is necessary to forbid all fatty foods, excluding even milk and eggs, for fat dissolves any phosphorus left in the stomach. The food should be albuminous. Other lines of treatment have for their object the oxidation of the phosphorus so as to render it inert, as, for example, the use of peroxide of hydrogen, a drug which is too unstable to be trusted. Duplos suggested liquor chlori, and Scherer chloride of lime; but experience has shewn that they act too slowly. Potassium permanganate freely diluted is a safe and fairly trustworthy oxidising agent, but it must be given early. The stomach should be washed out first with warm water and then with 2 per cent solution of potassium permanganate. Enemas of 1 per cent solution of the same salt may be administered, since the fluid rapidly passes up the bowel. Of 145 patients suffering from phosphorus poisoning thus treated by Plavec and others only 31 died, or 21 per cent. Oil of turpentine is the antidote usually employed; for its use we are indebted to Andant, who in 1868 was called to see a man who had attempted suicide by swallowing phosphorus paste, and to hasten the end had subsequently drunk turpentine. To the astonishment of both doctor and patient, not only were the symptoms slight, but the patient recovered. Bush of Dorpat has experimentally demonstrated how turpentine delays the toxic effects of phosphorus; and of fifteen dogs similarly poisoned by Personne, ten, to which turpentine was administered, recovered, while the remaining five died with the characteristic symptoms. Apart from its stimulating properties, it is maintained that phosphorus forms with turpentine a crystalline mass like spermaceti; but the only kind of it which is capable of doing this is the old French oil of turpentine, now with difficulty obtainable. The other two forms of turpentine—namely, the rectified and the German—have been shewn by Vetter's experiments upon dogs and rabbits to be useless. Ordinary commercial oil of turpentine in forty-drop doses, after the stomach has been washed out, still remains, however, a favourite line of treatment; and a fairly large percentage of cases thus dealt with recover. The efficacy of turpentine is increased by long exposure to the air. It is very desirable that the bowels should be cleared out by enemas or by gentle saline aperients.

Industrial Phosphorus Poisoning.—The number of people engaged in the manufacture of phosphorus in this country is small, probably not

more than 100; and as the greater part of the process is carried on under water there is no great risk to health. The most important industry in which phosphorus is largely used is in the making of lucifer and other kinds of matches. It is estimated that in England this industry gives employment to 2500 people. Phosphorus enters into the formation of ordinary wooden or congreve matches, wax vestas, and vesuvians. Certain departments in the manufacture are more injurious than others. The "composition" into which the ends of the matches are dipped contains phosphorus, potassium chlorate, and glue; and, occasionally, powdered glass, sulphide of antimony, manganese peroxide, and colouring matter. Not more than 5 per cent of phosphorus need be present in the composition. It is in the "mixing" of the composition, and in the "dipping" and "drying" of the matches, that noxious fumes are given off. In the manufacture of "safety" matches and in matches that come from Sweden no yellow phosphorus is employed. For ignition these matches have to be rubbed on a portion of the box covered with a dried paste, the principal ingredient of which is the harmless red or amorphous phosphorus. The entrance of phosphorus fumes into the system by way of the respiratory organs is followed by a slow intoxication called in France *phosphorisme*, of which cachexia, a yellow tint of the skin, garlicky odour of the breath, the presence of phosphorus in the urine and saliva, anæmia, abortion, a high rate of infantile mortality, albuminuria, and demineralisation of the tissues, are the most important symptoms; to these may be added cystitis, bronchitis, rupture of the muscles, and fragility of the bones.

Amongst match-makers one of the most serious consequences of the prolonged exposure to phosphorus fumes is disease of the jaw-bone. The work-people suffer from necrosis of the bone, sometimes called in this country "phossy jaw," and in France "mal chimique"; a disease which attracted considerable attention in Germany and Austria so far back as 1838, and which in our own country of late has been the subject of a departmental Government inquiry. The "mixers" and "dippers" are particularly liable to suffer from phossy jaw. The disease, though it affects both jaws, yet principally affects the lower; and the first symptom of it is toothache, which is not relieved by extraction. We cannot say definitely how phosphorus fumes act upon the bones. By some it is supposed that arsenic, which is frequently present with the phosphorus, causes the inflammation. Wegner experimentally produced necrosis of bone by the direct action of phosphorus fumes upon those portions where the periosteum had been exposed by dissection. Hence the greater liability for those persons to suffer who have carious teeth. It is supposed that the fumes enter the carious cavity and reach the periodontal membrane by the apical foramen. Operatives with decayed teeth have always been regarded as specially susceptible; although it has been lately maintained that the local inflammation is part of a general poisoning of the system. Mr. Hutchinson mentions a case where the prolonged internal use of phosphorus was followed by

characteristic necrosis of the jaw. Mears found that in the early stages of phosphorus necrosis there is an accumulation of tartar round the neck of the teeth, and that the disease is a chronic toxæmia with local irritation of the gums aggravated by decayed teeth and tartar. Cold readily excites inflammation in such gums, and this extends to the periosteum. Mears also noticed that the gums of cachectic operatives are the seat of small hæmorrhages. He considers that the poison enters the system by inhalation and also with the food, and that the toxæmia precedes the local affection; hence such primary symptoms as nausea, vomiting, and increasing debility. Beginning as an inflammation of the gum accompanied by toothache, or as inflammation of the periodontal membrane, it gradually extends to the periosteum, along which the process advances until a large part of the bony covering of the jaw is affected. This is followed by an osteomyelitis which ends in necrosis. As each tooth in the early stages is removed on account of pain it often happens that a small quantity of pus escapes from the alveolar cavity; the pus as it escapes frequently has the odour of phosphorus. The teeth become affected one after another until a large portion of the jaw is denuded of its periosteum.

Since phosphorus necrosis is said to have occurred in people whose teeth were perfectly sound, the gums in these instances must have been the parts first affected. Notwithstanding that several experimenters, as stated in these pages, have succeeded in producing necrosis of bone in animals exposed to phosphorus fumes, it is yet not an easy matter to produce the malady. Such at any rate is my experience. There is something peculiarly human in phosphorus necrosis, for men and women become rapidly affected by it compared with animals. Professor Stockman considers phosphorus necrosis to be not so much the immediate result of phosphorus as a tuberculous process, since in the pus escaping from the diseased jaw of a lucifer match-maker he found tubercle bacilli. Although on several occasions I have carefully examined the pus discharged in similar circumstances I have never found tubercle bacilli therein. I have had the privilege of examining Professor Stockman's slides, and am able to corroborate his statement as to the presence of a few tubercle bacilli. How far phosphorus necrosis, however, is to be regarded as solely a tuberculous lesion is another question. There is always the possibility of accidental infection, and besides there are several forms of micro-organisms present in the pus escaping from the diseased bone owing to its proximity to the mouth. Whether tubercle bacilli are alone responsible for the malady, whether phosphorus necrosis is the result of a mixed infection, or whether phosphorus in the form of fumes or as phosphoric acid, by acting upon the teeth and gums and inducing inflammation, prepares the soil for subsequent invasion by micro-organisms, and if so which particular type, are questions to which at present no answer can be given.

François Arnaud, from his position as medical officer to the match factories of Marseilles, has had unusual opportunities of studying the disease known as chronic phosphorism. Match-makers, he says, are readily

recognised by the peculiar odour which hangs about them and escapes by their breath. So strongly has their system become impregnated with the poison, that practically speaking all their excretions exhale an alliaceous odour. As might be expected, the prolonged elimination of phosphorus by the kidneys is followed by albuminuria in a large percentage of those whose work most exposes them to the poison. Their health, notwithstanding, does not deteriorate rapidly. The garlicky odour of the urine is regarded as a measure of the amount of the poison present, for it is as free phosphorus that this substance appears in the urine. Arnaud has never noticed the phosphorescence of the urine in the dark described by some observers. The output of urea is generally high, but phosphoric acid is not increased in quantity—this, as we have seen, is not the form in which phosphorus leaves the kidneys. Phosphorus appears so to act upon nutrition generally that if work-people are in good health metabolism is stimulated thereby; and not only is the amount of urea in the urine increased, but the inorganic constituents as well. Should anything arise, however, to disturb elimination, or should dental defects appear, the toxic effects of the element gradually appear.

Exposure to phosphorus fumes is doubtless the exciting cause of this malady; but, as already mentioned, depressed general health, an unwholesome condition of gums and teeth, and ill-ventilated workrooms dispose to it. Improved ventilation, reduction of the amount of phosphorus in the "composition," wearing of respirators in the drying-room, dismissal of all work-people who have bad teeth or who suffer from inflammatory affections of the gums, personal cleanliness of the workers, careful washing before eating, and the provision of meals outside the factory, are precautionary measures of the greatest importance. Since the substitution of sesquisulphide of phosphorus for the white variety in the manufacture of lucifer matches the match industry has become a comparatively healthy one.

The *treatment* of phosphorism and its cachexia should be directed towards the elimination of the poison. Exclusive milk diet, the inhalation of oxygen, gentle exercise, and repeated small doses of turpentine, are the agents recommended by Magitot of Paris, who has had a large experience of the disease amongst the French match-makers. In American factories the operatives, believing that turpentine vapour neutralises the fumes of phosphorus, carry wide-mouthed vessels containing the oil suspended by straps round their neck. The gums of the work-people should be regularly examined, and the presence of the slightest change therein should oblige the operative to cease work, and to use a mouth-wash of boracic or carbolic acid. Once suppurative periostitis is established an effort should be made to limit it by free incision and thorough drainage —washing out the sinuses with weak corrosive sublimate or carbolic acid—and giving the patient good food; but when this stage is reached necrosis is almost sure to follow. Although resection is the proper treatment for the necrosed jaw, surgical interference should be avoided so long as profound phosphorus cachexia remains; operation in these circumstances

is very apt to be followed by a recurrence which the surgeon cannot always control.

Mercury

Workers in mercury become poisoned by direct handling of the metal, by breathing it in the form of vapour or dust, or by absorption through the skin. When mercury is continually handled it tends to throw the skin into creases, within which fine particles of the metal become lodged and subsequently absorbed. Eating with unwashed hands conveys metallic particles into the gastro-intestinal tract, where, under the influence of the digestive juices, they become dissolved. The mercury used in this country comes from Spain as cinnabar or sulphide. From cinnabar the pure metal is extracted by simply roasting the ore alone, or by mixing it with lime or iron filings, when metallic mercury is given off and readily condenses. This process of extraction is dangerous to those employed. Work-people exposed to mercurial vapour at a very low temperature scarcely suffer: the danger increases with elevation of temperature; for having penetrated into the respiratory passages, the vapour, as the temperature falls, becomes condensed, and forms small droplets or granules which are deposited on the mucous membrane. These droplets become oxidised, and are therefore absorbed. When, on the other hand, the temperature in the workshop is low, the mercury, too heavy to remain suspended in the atmosphere, is deposited on the hair or beard of the workman, or upon his hands and clothes; and with this upon him he leaves the factory. Men who handle the metal, or who are engaged in the preparation of its salts, also run the risk of being poisoned by absorption through the lungs, creases or cracks in the skin, wounds, or the open sores which are the effects of the mercury. Add to these the habitually diseased condition of the gums, and the channels by which the poison may effect an entrance are many. It is difficult to say what reactions take place before mercury enters the circulation. The presence of common salt in solution or a free acid favours the dissolution of the metal. Corrosive sublimate forms with albumin an albuminate of mercury which, though insoluble in water, is readily dissolved in the presence of salt solution. Until lately water-gilders made use of mercury for depositing gold on metallic surfaces; and in mirror-silvering it was also employed. Water-gilding in this country has been largely supplanted of late by electro-plating. The silverers used to suffer considerably from mercurialism; but the silvering of mirrors, which is still an important industry, is now practically harmless to those employed in it, since the process by which metallic silver can be deposited on glass from the metallic tartrate has come into use. In barometer-making, bronzing, felt-hat making, skin and fur dressing, mercury, or its salts, such as the bichloride and acid nitrate, is used; and poisoning occurs occasionally. In what is known as "carotting," or the brushing of rabbit-skins with an acid solution of nitrate of mercury, the men lose the molar teeth in the upper and lower jaws. The teeth that remain are black, and are often

loose. From the action of the acid fumes the teeth become eroded, the enamel suffering, and not the dentine, as in caries. The gums recede, and lead to exposure of part of the anterior surface of the roots of the teeth. One of the most frequent consequences of industrial mercurialism is tremor of the limbs; and this may be the only manifestation of any effect upon the system. If work-people are exposed to the vapour at a high temperature, tremor is rapidly induced; hence the readiness with which it attacks those who are engaged in smelting the metal or in making amalgam. Eight per cent of the men thus employed suffer. Certain conditions have long been known to dispose to this form of poisoning; for example, want of cleanliness on the part of the artisan, deprivation of food, and the abuse of alcoholic stimulants. As far back as the early part of the last century Merat denounced the uncleanly habits of gilders, and earlier still Jussieu demonstrated that the convicts in the mines of Almaden, who lived continually therein, became a ready prey to mercurial tremor; the free miners, on the other hand, who lived in the neighbourhood and were careful to exchange their clothing and to eat only after washing, enjoyed health as good as other people in the district. Authors who have subsequently written upon the conditions of life at the mines of Almaden repeat this story. As late as 1886 Raymond, who had visited the mines, states that the work-people possessed of a good constitution who follow agriculture after their mining is done, and who lead regular lives, are almost never attacked; and if they are, then health is soon regained by desisting from work in the mine for a time.

In the ten years ended 1903 there were 85 deaths from mercurial poisoning in England and Wales—46 males and 39 females; of these, 31 males and 22 females were cases of suicide, mostly from corrosive sublimate.

Morbid Anatomy.—The internal lesions deserve notice. By whatsoever channel mercury has been administered, the intestine is generally found to contain large quantities of liquid of a yellow-brown or sanguinolent character; the bloody matter being most frequently in the neighbourhood of the cæcum and in the large intestine. There is extensive desquamation of the mucous membrane of the small intestine and cæcum, with hyperæmia and ecchymoses. It is difficult to explain the intestinal hyperæmia in mercurial poisoning. It may be due to altered blood-pressure, the existence of which Mering demonstrated, or, as Roy's experiments upon colchicum suggest, to an elimination of the mercury by the intestinal mucous membrane. The latter is the more likely explanation.

In one of Prevost's cases, that of a man poisoned by mercuric nitrate, the kidneys were the seat of a peculiar form of nephritis. The epithelial cells of the convoluted tubules were granular and opaque; in places the tubules were filled with compact masses composed of chalk. In subacute cases of mercurial poisoning decalcification of the bones occurs with a deposit of lime salts in the kidneys.

Although large doses of mercury cause deterioration of health, in very small doses the drug seems to act as a stimulus to nutrition. Many patients put on flesh when taking mercury; and their blood-making organs have their functional activity increased, as witnessed by the larger number of red blood-cells.

Mercury is eliminated by the kidneys and saliva, and by the milk of nursing women; whilst its insoluble salts pass out by the bowels. Like lead it is supposed to enter into combination with albuminous bodies in the tissues, there remaining inert, to be subsequently oxidised and returned to the circulation as an active poison. Mercury has been found in the urine and saliva two and four hours respectively after having been swallowed, and in the urine fourteen hours after having been applied to the skin. Although it is said to be thrown out of the system entirely and with some rapidity, mercury has been found in the brain, liver, muscles, and kidneys of animals. It is probable, therefore, that while a single dose of mercury is rapidly eliminated from the system, repeated small doses distributed over a long period are not regularly eliminated; hence more or less of it is deposited in the tissues.

Mercury is detected in organic substances and fluids by what is known as Ludwig's method. Urine is evaporated to dryness and then treated with hydrochloric acid; or the urine may be simply acidified and then heated to 50-60° C.: the suspected tissues are cut small and boiled in 20 per cent hydrochloric acid. To these granular zinc or finely divided copper is added, and the whole is shaken up well and then allowed to settle. After pouring off the supernatant fluid the sediment obtained upon a filter is well washed with boiling water and dried at 60° C. It is then placed in a combination tube of hard glass and covered with a plug of asbestos, upon which is placed a layer of granular oxide of copper. Another asbestos plug and layer of zinc previously dried and heated may be added. The tube is now drawn out into a thin capillary extremity and combustion made. The mercury is deposited as a metallic powder in the capillary tube. This portion is now broken off and a few particles of iodine placed in it whilst it is still hot. As the iodine vapour impinges upon the mercury scarlet mercuric iodide is formed which is at once recognisable by its colour. A readier test, after boiling with hydrochloric acid and water, is to place a piece of pure copper foil in the tube while the liquid is warm; if left for several hours it acquires a silvery lustre, from which globules of mercury are to be obtained by sublimation.

Symptoms.—The tremor, which may appear suddenly or slowly, is at first observed on movement only; but ultimately it becomes constant. It is usually limited to the face, hands, and arms, and is confined to certain groups of muscles. In some of the very severe cases the tremors may be so violent as to resemble violent chorea. The patient prefers to lie on the floor; he can neither clothe nor feed himself, and it is with difficulty that he gets more than short snatches of sleep, during which the trembling disappears. The powers of chewing and walking are affected. Speech may become slow and indistinct from involvement of

the muscles of articulation. In addition to the tremor there are frequently stomatitis with abundant salivation, and symptoms of gastric catarrh and diarrhœa followed by emaciation and paralysis. Like the salivary glands, the pancreas, seems to be readily influenced by mercury; hence the watery character of the stools and the large congested condition of this organ found after death. In some cases there is "wrist-drop," as in plumbism; a condition due, says Letulle, to degeneration of the sheath of peripheral nerves, the axis-cylinders remaining healthy.

Gingivitis, profuse ptyalism—the saliva being secreted to the extent of from one to two gallons a day, fetid breath, ulceration of the interior of the cheek with sloughing followed by cicatrisation or periosteo-alveolar swelling, fungous gums, decay and shedding of the teeth, conjunctivitis, and cachexia are observed in industrial mercurialism. Excessive salivation is frequently accompanied by a slight rise of temperature; and its progress is favoured by the existence of disease of the kidneys. The cachexia, which resembles that of scurvy, is characterised by great anæmia, debility, emaciation, loss of hair, pains in the muscles and joints, and œdema of the feet. There is a reduction in the number of the coloured corpuscles and in the albumin of the blood. Periostitis and enlarged glands may be consequent upon the state of the gums; and there may be skin eruptions of the nature of erythema, or eczema, followed by desquamation. Individuals thus affected frequently succumb to phthisis. The cerebrospinal system may become affected; the patient may complain of sleeplessness or giddiness, or of epileptiform seizures and paralysis—the paralysis differing from that met with in plumbism, in the persistence of the normal electric contractility of the muscles, the axis-cylinder of the nerves not being destroyed: the diagnosis is corroborated by the absence of a blue line on the gums, and the history of the occupation of the patient. The tremor resembles that observed in disseminated sclerosis and paralysis agitans. In disseminated sclerosis and in mercurialism the tremors appear during exertion, and cease when the patient is at rest or asleep; those occurring in hydrargyria are less wide and irregular, they are not accompanied by nystagmus, but by more pronounced stammering in speaking. In both diseases the tongue, when protruded, is tremulous. In paralysis agitans, on the other hand, the tongue is steady when protruded, and there is little or no oscillation of the limbs during effort; the tremors are observed even when the patient is at rest, they affect the wrist and fingers particularly, and the patient exhibits a peculiar forward gait, impelling him to pass from a walking to a running pace. As a distinguishing feature between mercurial tremor and that occurring in disseminated sclerosis Charcot pointed out that while the oscillations cease during rest it is in the former case in a remittent manner only; and they reappear from time to time without the patient making any movement spontaneously, or under the influence of emotion: whereas in insular sclerosis the tremor is completely absent during rest. There is also a superficial resemblance between mercurial tremor and general paralysis of the insane. In the latter the tremor is

never so pronounced; moreover the inequality of the pupils, the grandiose ideas, and the symptoms of spinal degeneration are not observed in mercurialism. Generally speaking, it is upon the nervous system that the poison exerts its most baneful influence. Two young men, assistants in the chemical laboratory at St. Bartholomew's Hospital, suffered severely after making mercuric methide. Besides emaciation and paralysis of motion and sensation, symptoms of acute mania set in, in the course of which one of the sufferers died; while the other, who never thoroughly regained his health, died a few months afterwards from pneumonia. Symptoms resembling hysteria may be met with, but these occur in people with a proclivity thereto; whilst in other cases vertigo, hallucinations, and insanity—a condition spoken of as "mercurial erethism" (Gowers)—mark the invasion of the cerebrum. Removal of the individual from the influence of the poison may be quickly followed by a subsidence of the acute symptoms. By the various emunctories mercury is eliminated from the system; nevertheless the process may be slow and extend over years. Kussmaul states that the children of workers in mercury are anæmic and ill-nourished; and that they frequently suffer from rickets and phthisis: also that women, if pregnant, miscarry and that the infant is still-born. Bäumler quotes the case of a man—a gilder—who, after following his occupation for twelve years, was obliged to desist on account of tremor, loss of memory, shedding of teeth, and so forth. He married three times. All his wives followed the occupation of gilding. By his first wife he had four children: one died of gangrene of the feet; the other three and the mother died of phthisis. By his second marriage he had two children, who, with the mother, died of phthisis. By the third union all the children born before the mother took to gilding remained well; but the one born subsequently died from a cause not stated, although the mother died of phthisis. In "sole stitching" by American machinery the men are said to have become mercurialised by volatilisation of the metal.

Medical men are compulsorily required to notify to the Home Office all cases of mercurial poisoning occurring in factories and workshops. Some persons are more susceptible to mercury than others, but all who are brought into contact with the metal or its salts when at work in the factory must submit to a periodic medical examination. Improved ventilation of the workroom has diminished industrial mercurialism. As additional precautions the use of sulphur baths, careful scrubbing of the body with soap and water, rinsing the mouth with chlorinated water, brushing the teeth, and the wearing of respirators containing a sponge that has been dusted with sulphur, or soaked in a dilute solution of silver nitrate, may be recommended. Iodide of potassium in small doses is regarded as a prophylactic, but it easily causes iodism. The internal administration of sulphur and plenty of milk are useful preventives. Experience has shewn that in factories in which periodic medical examinations by the certifying surgeon are made, and the workers are careful in keeping their mouths and teeth clean, it is unusual for symptoms of mercurial poisoning to

occur. When the gums have become soft and inflamed a mouth-wash composed of alum and potassium chlorate has been found useful.

Upon animals, as upon man, mercury exercises an injurious influence when applied to the skin; salivation and stomatitis occur, followed by paralytic phenomena. It has generally been supposed that when the metal is pure and swallowed in bulk it is non-poisonous; but in a case alluded to by Mr. Wynter Blyth tremor and loss of muscular power were seen. Occasionally profuse dermatitis, with desquamation, has been the consequence of administering mercury, therapeutically, by the skin: death, indeed, has followed the practice. The symptoms of mercurialism may be met with in any person, no matter by what channel the metal entered the system. In the case of the corrosive salts of mercury—for example, mercuric chloride or corrosive sublimate—the symptoms are immediate and very severe. Three grains have proved fatal. Death may occur within twenty-four hours. The patient complains of a sense of burning heat in the throat with a sense of constriction in the act of swallowing; the mucous membranes look pale and shrivelled as if they had been brushed with lunar caustic. Œdema of the glottis rapidly comes on, followed shortly after by death from asphyxia: or there is severe epigastric pain accompanied by repeated vomiting streaked with blood, and diarrhœa with bloody stools. The temperature quickly falls, the breathing becomes difficult, the pulse small and irregular, the urine scanty or completely suppressed; collapse supervenes, and death, which may or may not be preceded by convulsions, occurs. After death the whitened escharotic condition of the gastro-intestinal mucous membrane is very noticeable, with here and there ecchymoses and black patches due to the deposit of sulphide of mercury.

Similar symptoms have followed the internal administration of mercuric nitrate and its external application to the cancerous womb; and the more recent and extensive employment of the bichloride of mercury, as an antiseptic in surgery or as a uterine douche in midwifery, has been followed by symptoms of an extremely dangerous character. Of the antiseptic value of bichloride of mercury there is no doubt. Koch has demonstrated that 1 in 1000 parts of water will destroy the most virulent of germs in non-albuminous media. If albumin be present this becomes coagulated, and an albuminate of mercury is formed and deposited, which leaves the supernatant liquid free from the drug, and therefore without antiseptic power. Laplace, one of Koch's assistants, has shewn that this accident may be averted by the addition of a small quantity of acid. The acid sublimate is therefore the surest and most powerful antiseptic. In a solution so weak as 1 in 50,000 it is capable of destroying the microbes of pus.

Prevost has published the results of his experiments upon animals with various salts of mercury, administered subcutaneously or given by the mouth. The results, if the dose was fairly large, were diarrhœa, great debility, albuminuria with tube-casts, hæmaturia, collapse, and death within a few hours. When the dose was smaller the symptoms were the

same, but less severe; they were accompanied by rapid emaciation and death within a few days. As in arsenical poisoning, the symptoms appeared equally when the mercury was injected subcutaneously or given by the stomach; but a smaller dose sufficed when given hypodermically. In some of Prevost's animals death supervened within a few hours after the subcutaneous injection of the peptonate of mercury, and was apparently due to paralysis of the heart; as the end came before there was time for any lesions of the internal organs. The blood, too, was dark and diffluent, similar to that observed when arsenic, platinum, or silver nitrate has been injected. In v. Mering's experiments the kymograph registered a very rapid and progressive fall of the arterial pressure, even after the administration of atropine or section of the vagi—a proof that the diminished arterial pressure was due to cardiac failure.

Treatment.—Ptyalism is relieved by mouth-washes of myrrh and potassium chlorate, with tonics internally. The treatment of acute mercurial poisoning consists in encouraging the vomiting, usually present, by means of apomorphine in four-drop doses hypodermically administered; or by sulphate of zinc given by the mouth. Generally the vomiting is such that these emetics are unnecessary, as also the use of the stomach-tube, so needful in other forms of poisoning. In all circumstances the administration of diluent drinks containing white of egg is called for. If there be much pain, opium or morphine may be given. In the slow forms of poisoning the symptoms must be dealt with on general principles. The nutrition of the system must be carefully attended to. Potassium iodide may favour the elimination of the poison. For mercurial tremors phosphide of zinc in pill form, $\frac{1}{10}$ to $\frac{1}{4}$ of a grain, is recommended to be taken twice or thrice daily.

Copper

Copper is widely distributed in nature. It is found in several soils and in spring and river water; occasionally in wheat and turnips, in other articles of food and drink, and in the blood of several of the invertebrates. According to Dr. Dupré it is frequently present in small quantities in the liver and kidneys of man, but more particularly of ruminants. The use of copper cylinders and boilers in cooking is one source by which food and drink may become adulterated. Salts of the metal are occasionally employed to impart a green colour to preserved vegetables, such as green peas, so as to render them attractive to the eye; and in France they are added to absinthe to improve its colour. Cupric sulphate is administered internally as an emetic; it is given in very small doses as a tonic to the nervous system, and is used in diarrhœa as an astringent. Applied in a weak solution externally to wounds it acts as a stimulant and astringent; but beyond these purposes the metal is little employed in medicine. A considerable amount of copper is present in ordinary bronzing powders for lithographic purposes; and it is a large ingredient of the powders which are used for the lilac and purple fires of the pyro-

technist. Horses and cattle can take large doses of sulphate of copper (2 drachms or more) without any apparent bad effects; but the same quantity has caused very serious symptoms in the human subject. When administered by the mouth it acts as an irritant poison, causing violent and persistent vomiting, depression of temperature, and death from respiratory failure; but when given hypodermically vomiting is not induced.

Symptoms of copper poisoning in man appear shortly after the drug has been swallowed—in from one quarter of an hour to two hours: these are, a metallic taste in the mouth with salivation, severe vomiting of green-coloured matter, colic, and purging; the stools contain glairy mucus and blood, and if the dose has been large, death follows these symptoms in a few hours. It is often preceded by convulsions and delirium, paralysis, syncope, scanty or suppressed urine, and hæmoglobinuria. Should a fatal termination be warded off for the time being, jaundice, followed by great nervous depression, may supervene. In fatal cases there is well-marked gastro-intestinal inflammation with numerous ecchymoses; and the liver is observed to be fatty.

In the **treatment** of acute copper poisoning milk and eggs are efficient antidotes. Eggs should be beaten with water or milk and administered freely so long as vomiting continues. The alkali which is present in soap renders this commonplace article also useful as a means of treatment. Pure prussiate of potassium precipitates copper from its solutions, and in small doses may prove beneficial. After antidotal treatment has been tried, opium in small doses may be needed for the relief of pain.

As an **industrial disease** poisoning is practically unknown in the copper-works on Tyneside; nor does occupation in the copper-works appreciably influence any disease that the individual may subsequently suffer from. Occasionally a metallic taste in the mouth and colic are complained of; but I have seen nothing of the vomiting, diarrhœa, and wasting mentioned by some authors. In this I am confirmed by Houlés, who has studied the condition of life in a village full of copper-workers, where for the last four hundred years this industry has been carried on: sons succeeding their fathers, so that an ancestral integrity has been established. In spite of their long hours of toil in an unhealthy atmosphere, of green lines on their teeth and green hair, the men, though not robust, are healthy, the average age at death being 60. Not only is the metal found in their secretions, but long after death their bones when raked up are green. In copper-workers the gums are discoloured and ulcerated, and the teeth, especially the incisors and canines, are green. On more careful examination, however, it is observed that it is not so much a distinct line of coloration that is present on the gums, as a deposition on the tartar and enamel of the teeth which is easily removed by brushing. Occasionally in old copper-workers the inflammation and ulceration of the gums lead to the exposure of a considerable length of the teeth. The coloration is due to the deposit of particles of copper upon the teeth and their chemical combination with associated

matter. Copper has, apparently, none of the serious effects upon work-people that lead and arsenic have; but symptoms generally appear if the copper is combined with zinc as in brass-moulding. Galippe took fairly large doses of copper for one month without any bad effects; and, as dogs to whom the metal was administered did not suffer, it is evident that considerable quantities may be passed into the system without causing much injury. Du Moulin experimented upon himself and family with a similar result. A knowledge of these facts has influenced to a large extent the verdicts of courts of law in regard to the adulteration of food and tinned vegetables by copper; but whilst on the Continent public opinion is disinclined to regard artificially coloured vegetables as dangerous, in this country several convictions have taken place. So fully convinced is the French Government of the harmlessness of vegetables coloured green by cooking in copper vessels that in 1889 it revoked the law applying thereto.

Copper is therefore regarded by many as not a dangerous metal. The experiments conducted by Laborde, however, clearly indicate that it is not only an irritant poison when given by the stomach, but a cardiac and muscular poison when administered by intravenous injection. It is required of copper, perhaps, more than of other metallic poisons (in contradistinction to those of an animal nature) that the dose must be large; and as vomiting is sure to follow, it is by this means at once expelled from the system. In cases where copper has been given in solution and upon an empty stomach absorption has taken place—for the metal has been found post-mortem in the liver, kidneys, lungs, and blood, which on the addition of ammonia give a blue colour indicating the presence of the poison. Admitting that traces of copper may be found in the liver and kidneys of people who during life seemed healthy, and that a kind of tolerance had been established, it must be acknowledged that beyond a certain point the salts of copper are toxic. To produce serious symptoms, however, large doses are required, say 40 to 60 grains of copper sulphate repeated in a few hours.

Men who are engaged in making sulphate of copper take little or no harm; there is, practically speaking, no absorption of the drug. A malady known as "*brass-founders' ague*" is met with amongst those who are engaged in making mouldings of copper, bronze, and brass. Millon as far back as 1847 found that coppersmiths suffered. In 1862 Greenhow drew attention to brass-making as a cause of ill-health amongst the work-people. Previous to both of these writers it is true that Thackrah had written upon the relationship of intermittent fever and brass-founding; but it is to Drs. Hogben, R. M. Simon, Arlidge, and W. Murray of Birmingham that we are indebted for a full account of the malady. In brass-making, copper and zinc and small quantities of lead, tin, and brass-dust are melted together; and it is during the act of pouring this compound from the crucible into moulds that the zinc deflagrates. A dense white cloud of oxide of zinc fills the atmosphere and collects upon the rafters and ceiling of the workshop in the form of a white incrusta-

tion. It is notorious that the men, who are called "mixers," and who even try to protect themselves by wearing respirators, suffer considerably in ill-ventilated shops from ague and bronchitis. Those who remelt the pig-brass, and are called "founders," also suffer from bronchitis and asthma, but less severely from ague; although from the molten compounds clouds of zinc are given off. The metal after being polished is sent to the "dippers," who work in an open shed: they dip the brass first into a weak and then into a stronger solution of sulphuric acid and soda; afterwards it is placed into pure sulphuric acid, and washed. These men do not suffer from ague or intestinal troubles; but it is admitted that the work is dangerous to health from the great bronchial irritation caused by the acid fumes. According to Dr. Simon it would appear that those who are engaged regularly at brass-making do not suffer from ague; it affects rather those who are new to the work, or who have absented themselves from it for a time. Thus, a degree of tolerance seems to be established towards it. In a newcomer the exposure of a few hours to the molten metals suffices to produce the ague. The individual soon becomes languid, depressed, and cold; he is pale and collapsed, his face is covered with a cold perspiration, he shivers, his teeth chatter, headache, nausea and vomiting follow, and after this there usually comes relief. The hot and sweating stages of ague, if present, are scarcely recognisable. In no manner, therefore, can this attack due to metallic poisoning be compared to malarial ague. The teeth of the men, in spite of the use of the tooth-brush, are always discoloured green. The white hair of the work-people is frequently coloured green. Although this so-called ague is of common occurrence, the men seldom go to hospital on account of it. They know how to treat themselves. Some of the men who are engaged in the dusty part of the factory ultimately succumb to chronic bronchitis and fibroid phthisis. The records of their own Benefit Society shew that they are a short-lived body of men. Nervous disorders also occur with considerable frequency amongst them. Drs. Suckling and Schlockow allude to the frequency of ataxia, and Hogben to progressive paresis of the legs, tremor, and muscular wasting as also occurring in them. Brass-workers suffer from gastro-intestinal disturbance, nausea, vomiting, a metallic taste in the mouth, colic, constipation or diarrhœa, headache, and muscular pains—a series of symptoms which I have also observed in men who work in boot and shoe factories, and who whilst engaged in soling boots hold brass nails in their mouths. These men become pale, and are frequently the subjects of colic and gastro-intestinal trouble.

It is difficult to say how far the symptoms met with amongst brass-workers are due to copper or zinc. Sir Thomas Stevenson maintains that it is impossible to distinguish between zinc and copper poisoning. Greenhow believed that the symptoms were due to zinc, Hogben to copper; whilst Dr. Simon regards the ague symptoms as due to the admixture of the metals, and the more chronic complaints as due to the copper. The workmen themselves have found out that milk is the

remedy during the attack of ague; but industrial prophylaxis—such as complete ventilation, the wearing of respirators, and personal cleanliness—is imperative. In chronic brass poisoning with laryngeal and bronchial symptoms potassium iodide has been found serviceable, while in ordinary cases phosphoric acid or minute doses of phosphorus taken thrice daily usually relieves symptoms with great rapidity.

For the detection of copper the text-books on toxicology may be consulted. It is sufficient here to mention that with fluids containing copper—(i.) ammonia gives a blue colour; (ii.) ferrocyanide of potassium a brown-red colour or precipitate; (iii.) the addition of tartrate of soda and sodium hydrate, and boiling with a few grains of grape sugar, give a red precipitate of oxide of copper; and (iv.) a needle, or the clean wire of a galvanic battery, if immersed in the suspected fluid, soon becomes coated with a red metallic film.

In certain bacterial diseases copper is a prophylactic. It is actively germicidal to typhoid and colon bacilli. Dilute solutions of copper salts have been found to be destructive to bacteria other than the above. A. H. Stewart found that in three hours the number of germs in raw tap-water would, if kept in copper vessels, fall from 384,000 to 18,000 per cubic centimetre, and that water containing colloidal copper has a more rapid action on typhoid organisms than upon those present in river water. In epidemics of typhoid fever, water can be purified of typhoid organisms by allowing it to stand in copper vessels for three hours. Experience has demonstrated the harmless effect upon health of copper-treated drinking-water.

Zinc

Accidents occasionally follow the use of zinc salts, especially of the chloride and sulphate. For years past experts have been in search of a pigment as a substitute for the white carbonate of lead so freely used in painting; and both the sulphide and oxide of zinc have been recommended. This subject was carefully inquired into by the White Lead Commission: and whilst it is admitted that for internal decorative purposes oxide of zinc gives on the whole satisfactory results, it has not the covering power, the permanence, nor the resistance of white lead to extremes of temperature and inclement weather. In France it has been decided to substitute zinc oxide for white lead wherever practicable. Zinc white (oxide) is used in calico printing, in the decoloration of glass, and in the manufacture of artificial meerschaum pipes. As zinc is largely present in vessels in which food is sometimes cooked, contamination of the food may occur; for the metal on being exposed to the air becomes coated with a film of oxide of zinc which, though insoluble in water, becomes readily soluble if a trace of chloride of sodium be present. The presence of chlorides generally favours the solvent action of water upon zinc, whilst carbonate of lime diminishes it. Milk may thus become readily contaminated. Milk contained in zinc vessels does not

become sour, probably because the zinc oxide combines with the lactic acid forming the very sparingly soluble lactate, and thus withdraws from the milk the lactic acid upon which its souring depends. According to Harnack zinc salts produce paralysis of the cardiac and voluntary muscles. The oxide of the metal in the proportion of 0·08 gramme to 0·04 kilo of the animal may cause death in rabbits. In my own experiments zinc oxide was administered to animals over a very long period, and in considerable doses; but when the drug was perfectly pure there were none of the rapidly fatal results which Falck and others described. One of the reasons why zinc oxide has been so strongly recommended to house painters is its harmlessness compared to lead carbonate. I am not prepared to say that zinc white is absolutely innocuous; but rabbits take it by the mouth for many months without seeming to suffer much discomfort; and in the mixing department of large colour-works men who breathe the dust and whose clothes are covered with the white powder do not, as a rule, suffer any inconvenience. It may seem to cause headache, nausea, vomiting, and cramp-like pains in the limbs; but as zinc oxide is frequently impure, containing small quantities of lead and arsenic, these symptoms are more probably due to the adulteration than to the metallic compound itself. Spelter workers in this country—that is, men who smelt zinc ore—occasionally suffer from plumbism, due to the small quantities of lead which the ore contains; but there are few or no bad effects from the pure zinc fumes. Zinc smelters, according to Schlockow, rarely live beyond the age of forty-five years. They frequently die from catarrh of the bronchial or pulmonary mucous membrane accompanied by peculiar nervous symptoms, beginning with burning sensations and heightened reflex excitability in the legs, and followed by signs of myelitis.

Death from chronic zinc poisoning, or from the sulphate, is extremely rare. However irritant a poison the latter may be, it is such a strong emetic that by means of the vomiting which it causes its elimination is at once accomplished. Sulphate of zinc, to the extent of one ounce, has been taken by mistake for Epsom salts. The patient suffered from violent vomiting and purging, severe cramps in the legs, and great prostration; but he recovered. The salt has, however, caused death, the symptoms being vomiting, purging, collapse, and death in thirty hours. Subsequently zinc was found in the stomach, liver, and spleen. Penfold relates the case of a girl who died $3\frac{1}{2}$ hours after taking sulphate of zinc to produce abortion.

Zinc chloride is a stronger poison, and is capable of killing by its primary and secondary effects. It has a powerful affinity for water, and dehydrates the tissues with which it is brought into contact; to this peculiar influence its caustic action is due. Burnett's disinfecting fluid, which contains large quantities of zinc chloride, has been a frequent cause of poisoning in this country. Death has followed the repeated external application of Canquoin's paste—a mixture of zinc chloride, flour, and water—as a cure for cancer; the symptoms observed during life

being those met with in zinc poisoning, namely, a burning pain in the lips, tongue, and throat, excessive salivation, bloody vomit, diarrhœa, collapse, and death within a few hours. When death has not rapidly followed, a peculiar group of symptoms has arisen; for example, a perverted sense of taste and smell, aphonia, spasms of the voluntary muscles, great fatigue, and impaired vision. A dose of 6 grains of zinc chloride has caused death, while as large a quantity as 200 grains has been recovered from. Zinc chloride may be present in canned vegetables, owing to zinc dissolved in hydrochloric acid having been used for soldering the tin.

Morbid Anatomy.—When sulphate of zinc has proved fatal there have been evidences of inflammation of the stomach and bowels, accompanied by a peculiar tripe-like wrinkling of the mucous membrane; whilst the surface presented a uniform dirty grey colour. In death from chloride of zinc the lining membrane of the mouth and throat is white and opaque, the stomach is hard and leathery, congested or ulcerated. When the fatal issue has been postponed for a time cicatricial contraction of the œsophagus and stomach has occurred.

The **treatment** of the acute poisonous symptoms due to zinc salts consists in the administration of eggs and milk, tannin or green tea; and in the allaying of gastric irritability. The more chronic symptoms must be treated on general principles as they arise.

For the detection of zinc in organic liquids or solids the elaborate methods described in text-books on chemistry and toxicology must be used

Antimony

In this country there are very few antimony works; of these one of the largest is on Tyneside. Here large quantities of sulphide of antimony, the raw material that comes from the mines of Japan, are smelted along with iron filings; the result being sulphide of iron and pure antimony. The men who smelt the ore suffer no bad effects, practically speaking, from the fumes of the metal. The workmen are not brought into such close contact with the molten metal as in the smelting of some other ores; besides, the industry is carried on in well-ventilated shops. The only trouble, and it is more of the nature of an inconvenience, that is felt by the men is that as their work is hot and they perspire freely, the skin is extremely liable to become the seat of an herpetic eruption, at first vesicular, subsequently pustular, and excessively itchy. This eruption, which is called by the workmen the "pox," occurs where the skin perspires most freely—behind the neck and along the upper part of the abdomen. Eulenburg states that workmen who have long been exposed to the fumes of the oxide of antimony suffer from vesical and urethral pains, and atrophy of the testicles leading to impotence. Several of these men whom I have examined were pale; but only one or two of them had suffered from colic and gastro-intestinal disturbance, and this

very slightly. Antimony smelting does not, therefore, appear in itself to be a dangerous industry. The pure metal is employed for making printers' type—in the finishing of which, however, the dust is inhaled, which is said to cause colic exactly resembling that of plumbism. Probably this is due rather to lead, which is present in type-metal, than to the antimony itself. Mr. Pond of Liverpool and Dr. J. C. Thresh have drawn attention to an unexpected source of chronic antimony poisoning, viz. the use of india-rubber rings on bottles containing aerated beverages Rubber has been found to contain 15 to 25 per cent of sulphide of antimony. From rubber rings that have become worn the metal is more easily dissolved. As much as 1 milligramme ($\frac{1}{70}$th grain) to 0·7 milligramme ($\frac{1}{100}$ grain) has been recovered from a solution in which rubber had been soaked. Mr. Pond is of the opinion that the daily ingestion of small quantities of antimony sulphide in these circumstances is a cause of appendicitis and gastro-enteritis with possibly ulceration. Mr. Pond's views as regards appendicitis require confirmation.

Of the antimonial salts, tartar emetic—a tartrate of potassium and antimony—is the most important. Two grains of this have proved fatal to an adult, and two-thirds of a grain to a child. Horses and cattle exhibit a wonderful tolerance of the drug: they can take from 60 to 90 grains three times a day without much inconvenience. Whether tartar emetic be administered to man or the lower animals, by the mouth or subcutaneously, the effect is the same—vomiting takes place, and the heart's action, which is at first quickened, becomes slower and paralysed, probably from the direct action of the drug upon the heart.

When given in small doses to animals, and for a long time, diarrhœa, great hebetude, loss of appetite, and emaciation have been observed; pregnant animals have miscarried. Death has been preceded by convulsions, and small ulcers have been observed in the mouth. In man the symptoms resemble those produced by arsenic. If the dose of tartar emetic has been large, vomiting may not occur, or it may be accomplished with difficulty: there may be violent pains in the abdomen and purging, with rigidity of the muscles of the abdomen and arms, followed by profuse perspiration, continuing for several days. Applied to the skin in the form of ointment it may give rise to a pustular eruption and be followed by vomiting and purging.

If very small doses be given for a long time a metallic taste in the mouth is complained of, also frequent vomiting—the vomit being sometimes bloody—great faintness and bodily weakness, pains in the abdomen, and diarrhœa. Should the case advance to a fatal termination death is often preceded by suppression of urine, a marked fall of the temperature, cyanosis of the face, delirium, and convulsions. Frequently there is a pustular eruption on the skin. The Palmer and Pritchard trials demonstrated that even medical men might mistake the symptoms of chronic antimony poisoning for natural disease—the symptoms being nausea, vomiting, chronic diarrhœa alternating with constipation, a small, frequent pulse, loss of voice, great muscular weakness, coldness of the

skin, and clammy perspiration. In other cases flushing of the face with mental excitement, suggestive of mild alcoholic intoxication, has been observed.

Morbid Anatomy.—The post-mortem appearances met with in poisoning by tartar emetic are inflammation of the stomach and intestines, with small ulcers and pustules; or larger ulcers that are sloughing. The solitary glands of the intestine may be enlarged and yellow, whilst the liver, kidneys, and heart shew fatty change.

Like the other metallic poisons antimony is eliminated by the urine; hence in cases of suspected antimonial poisoning the urine of two or three days should be collected, concentrated by evaporation, and acidified with hydrochloric acid. This fluid is subsequently transferred to a platinum dish in which is placed a slip of zinc or tinfoil. By means of ammonium sulphide the antimony is dissolved out as the yellow sulphide. For more complete analyses Reinsch's or Marsh's tests may be employed.

Towards antimony people exhibit a peculiar idiosyncrasy. Some are easily affected by the minutest dose, others are extremely tolerant of it. It is well to remember that, as tartar emetic rapidly leaves the body by vomiting and purging, only the smallest trace of antimony may be found in the body after death; a fact of which lawyers engaged for the defence in criminal cases are apt to make the most.

Treatment.—As poisoning by antimony is generally due to tartar emetic it is more than probable that the patient will have vomited freely: if not, the stomach-tube must be employed. Once the stomach is thoroughly washed out there should be passed into it some strong infusion of tea or tannin. Should vomiting not have occurred, or the stomach-pump be inaccessible, a hypodermic injection of apomorphine, $\frac{1}{10}$th of a grain repeated every ten minutes, or $\frac{1}{4}$th of a grain at a single administration, is called for. Subsequently demulcent drinks are of great service. As considerable bodily depression and a fall of the temperature are apt to take place, the heat of the body must be maintained by the application of hot bottles and warm blankets, and the administration of stimulants by the rectum. Should signs of cardiac failure be present, the application of the interrupted galvanic current to the chest must be resorted to.

There is a form of antimonial poisoning in which, according to Husemann, neither vomiting nor purging occurs; where the symptoms are those of intense prostration as indicated by a cold clammy sweat, embarrassed and infrequent respiration, feeble, slow, and intermittent pulse; and in which delirium, tremors, or convulsions followed by unconsciousness appear, or the patient, after protracted vomiting and purging, dies from sheer exhaustion. For such cases stimulants and subcutaneous injections of ether are necessary.

Industrial poisoning from antimony hardly ever occurs. Working in well-ventilated "shops," attention to the state of the bowels, regular living and temperance, and personal cleanliness on the part of those engaged in smelting the antimony ore, are desirable; and for the skin eruption or

"pox" as it is called—which is due to excessive perspiration—sponging with a solution of bicarbonate or biborate of soda, or of boracic acid and bismuth, is generally sufficient to give relief. Abstention from work might be necessary.

Carbolic Acid

Carbolic acid is obtained from phenic acid or phenylic alcohol, a product of coal-tar distillation. It is used in the manufacture of dyes and salicylic acid. Although known in 1834, it was not until 1863 that Lord Lister introduced it into surgery, since which time it has become widely used as a disinfectant. Being thus so easily within the reach of the public, carbolic acid poisoning had, until its sale to the public was restricted, become extremely common, particularly among women. The history of carbolic acid poisoning is comprised within our own times. From the first recorded case of accidental poisoning in 1864, and of two suicides in 1869, there has been a rapid increase in the annual number of deaths from this cause. In the five years ended 1870, suicide by carbolic acid first appears in the Registrar-General's Reports to the extent of 1·0 per cent of all suicides by poison. In the quinquennium ended 1875, 128 deaths are reported, nearly 25 per annum; 42 of these are suicidal, 23 females and 19 males. It was in this period that the Public Health Acts were passed (1872-1875), and, as a consequence of the general interest aroused in sanitation, carbolic acid, then regarded as a reliable disinfectant, came within easy reach of the people, and began to serve as a means of self-destruction. An increase of 135 per cent occurs in the number of deaths by this poison during the five years ending 1880, the deaths being 181, of which 81 (53 females and 28 males) were suicidal; that is, 7·8 per cent of the suicides from all poisons. In the quinquennium ended 1885, 302 deaths from carbolic acid poisoning are registered, of which 191 (99 females and 92 males) were self-caused; that is, 15·6 per cent of all suicidal poisonings. For the five years ended 1890, 342 deaths are recorded, of which 215 were suicidal; an average of 43 per annum, and 15·4 per cent of all suicides by poison. During the four years ended 1894 the number of deaths from carbolic acid poisoning had still increased: 549 deaths having been reported, of which 420 or 76·5 per cent are suicidal, equal to 105 annually. The history of carbolic acid poisoning is a gloomy record, for whilst in the period 1861-65 the suicides by carbolic acid were 0·00 per cent of all suicides from poisons; they formed in 1866-70, 1 per cent; in 1871-75, 5·82 per cent; in 1876-80, 7·93 per cent; in 1881-85, 15·37 per cent; in 1886-90, 15·49 per cent; and in the quinquennium ended 1904, 26·66 per cent. According to Dr. John Tatham there were registered in the quinquennium ended 1904 833 deaths from carbolic acid poisoning, 410 males and 423 females. Of these, 334 males and 361 females—together 695 persons or 83 per cent—were cases of suicide. Carbolic acid stands first on the list of agents causing death by poison in the quinquennium ended 1904.

Since the introduction of the intestinal antiseptic treatment for the various forms of auto-intoxication due to the absorption of poisons elaborated within the alimentary canal, carbolic acid pure, or in combination with soda as sulpho-carbolate, has been freely prescribed. Of the beneficial effects of this line of treatment there is no doubt. The drugs should be given with a certain amount of care, and not for too protracted a period, as the urine may become discoloured and the patients complain of much malaise. In the early days of antiseptic surgery, when the carbolic spray was employed in cases of ovariotomy, it was no uncommon thing for those assisting at the operation to suffer from headache, a general feeling of malaise, altered sensibility of the skin, and occasionally vomiting.

Morbid Anatomy.—In animals killed by carbolic acid the post-mortem appearances have occasionally been simply an intense injection of the alimentary and bronchial mucous membranes, and congestion of the lungs. The cells of the liver and kidneys undergo fatty change. In man similar appearances have been found after death. The mucous membrane of the mouth, œsophagus, and stomach may present numerous white spots, with occasionally a dark centre and an inflammatory border, due to the local action of the poison. The liver, kidneys, and spleen may be congested and filled with dark liquid blood. In one of my male patients who died on the 8th day after swallowing an ounce of carbolic acid the vomit on microscopical examination shewed numerous large flattened epithelial cells, extremely fatty, which had evidently come from the mouth and œsophagus; and similarly in the urine, in addition to masses of débris, were many round cells, shewing marked fatty degeneration. The urine, although albuminous, contained a normal percentage of urea. On the fifth day several sloughs of gastro-intestinal mucous membrane two inches in length and of a yellowish-brown colour were passed by the anus without any bleeding. The day before death the heart rapidly dilated, a mitral systolic murmur appeared, and the sounds became extremely feeble.

Symptoms.—Carbolic acid causes severe symptoms whether swallowed by the mouth, breathed as vapour, administered in enema, applied to the broken skin, or taken in large doses in the form of carbolate of soda. Less than half an ounce of pure carbolic acid has proved fatal. The dark carbolic acid of commerce owes its colour to such impurities as cresol and cresylic acid—substances which render it stronger as a germicide, but only one-fourth as poisonous to the higher animals. When a strong solution of carbolic acid is applied to the skin it causes a peculiar numbness, followed later by irritation, and usually by a pustular eruption or desquamation of the skin, which, white at first, afterwards becomes brown. Messrs. Clement Lucas and Lane have reported two cases in which coma and other serious symptoms arose from the application of a 1 in 20 solution to the skin; and similar effects have followed the washing out of empyemas and large abscess cavities. After a few days' successive washing out of the pleural cavity symptoms of poisoning have

compelled suspension of the treatment. The application of strong carbolic acid to the interior of the uterus and cervix uteri in one of my own patients caused extremely unpleasant symptoms, accompanied by a rise of temperature; and similar but more severe symptoms were observed in obstetric practice by Küstner, on washing out the uterus with a 5 per cent solution of carbolic acid. The patient became livid, clonic convulsions supervened with temporary loss of consciousness, and death followed on the ninth day; the uterus and vagina were the seat of an intense membranous inflammation. It has been conclusively demonstrated that women who have lost large quantities of blood, or who are the subjects of septic fever, are peculiarly sensitive to the influence of carbolic acid: so likewise are children. The effects of the acid upon animals are similar to those observed in man. Crude carbolic acid applied accidentally over a large part of the skin has caused extensive burns, rapid unconsciousness and death in a few minutes.

If a large dose has been swallowed there is complaint of burning in the mouth and throat; the patient feels faint; the face becomes pale and covered with clammy perspiration; unconsciousness and perhaps convulsions gradually supervene; the breathing becomes shallow and laboured, and death comes soon after from respiratory failure, the heart beating for a few minutes after breathing has ceased. Resuscitation in some cases may be still effected by artificial respiration. The vomit is frequently bloody and smells strongly of the poison. The lips are dry and frizzled; the tongue is white or brownish; the patient cannot allow the epigastrium to be pressed on account of pain. The temperature tends to fall at first, but it may rise within the next few days and the patient may complain of an intolerable thirst. The urine from a case of carbolic acid poisoning may be normal. Much more frequently it is yellow when passed; gradually it becomes dark olive, and finally dark brown or blackish-green. If treated with nitric acid and then with liquor potassæ, it becomes after concentration blood-red in colour, and changes through pea-green to violet; a fact of some importance, for on the simple addition of carbolic acid to urine the mixture does not respond to this test. It may or may not contain albumin. In any case where such a discoloured urine has been passed by a patient who is the subject of coma or convulsions, the diagnosis of carbolic acid poisoning may be made with certainty. According to Baumann the darkened colour of the urine is due to the fact that when carbolic acid is taken internally it is eliminated as phenyl sulphuric acid or, more strictly speaking, as potassic phenyl sulphate; and from this hydroquinone and pyrocatechin are formed, which on exposure to the air become dark brown by oxidation. According to Prof. Halliburton, pyrocatechin, like sugar, has the power of reducing alkaline solutions of copper salts. Thudichum states that after the ingestion of carbolic acid a blue pigment is found in the urine. The blood of animals poisoned by this acid presents nothing abnormal; so that whilst the colour of the urine suggests the presence of altered blood-colouring matter or hæmatin, chemical facts do not support this supposition.

for the urine clears up on heating after adding an acid. Sir Thomas Stevenson states that the urine does not contain more than the normal proportion of iron; and Brieger maintains that when carbolic acid is taken internally it unites with sulphuric acid, and various coloured oxidation products are formed, some of which are very poisonous. Chemical opinion, therefore, leans to the view that the acid when swallowed enters into sulphuric acid relationships, and that the tendency is for the ordinary sulphates to disappear from the urine. Sometimes the fæces have the odour of phenol, and are dark olive-green in colour. Hoppe-Seyler, Nencki, and Brieger believe that carbolic acid is a constituent of normal urine, and that it is present also in the fæces, its source being the tyrosin obtained from proteids acted upon during pancreatic digestion.

Since carbolic acid coagulates albumin, absorption of the drug has been questioned; yet there is considerable evidence to shew that it is absorbed; it is eliminated as such in the urine, which also contains numerous oxidation products derived from it. We do not exactly know the form in which it circulates in the blood, but it is probably as an alkaline carbolate. It is retained for a short time only within the system, being rapidly thrown out in the excretions.

Diagnosis.—In cases of acute carbolic acid poisoning there is generally a distinct odour of it in the breath; this, with the presence of white patches on the lips and mucous membrane of the mouth, and, later, the altered colour of the urine, are sufficient to point to the real nature of the illness. As in some cases neither discoloration, whitening, nor congestion of the lips and buccal mucous membrane are observable, the medical attendant may be thrown off his guard unless he has a history of the case to guide him, or a phial is found containing poison.

Treatment.—The use of the stomach-tube and washing out are immediately called for. Emetics are of little service, for, owing to the anæsthetic state of the stomach, they fail to obtain a response. Whilst the administration of alkalis in excess is useful, Baumann and Hueter have shewn that the antidote to carbolic acid poisoning is a soluble sulphate; for during this form of poisoning sulphates disappear from the urine, and if a soluble sulphate be supplied it enters into combination with the acid, forming the less harmful sulpho-carbolate which is rapidly eliminated. Other writers, notably Sonnenburg and Cerna, have confirmed the value of alkaline sulphates in the treatment of acute carbolic acid poisoning. The former found that the dark colour of the urine and other symptoms rapidly disappeared under the administration of sodium sulphate; and Cerna in his experiments upon animals had equally good results from the administration of magnesium sulphate. But these alkaline sulphates, to be efficacious, must be exhibited freely. Schobert recommended saccharate of lime as an antidote to phenol poisoning, so long as the poison is still in the stomach; after it has passed into the intestine he gives sodium sulphate. The saccharate of lime he prepares thus:—Fresh quicklime, 15 parts; Sugar, 25 parts; Water, 1000 parts: and of this mixture fairly large quantities may be administered. In one

of my own cases, where consciousness was long in returning, we transfused the patient with saline solution, containing sulphates, in the hope of forming harmless compounds and of washing out the poison by the kidneys. Two days afterwards the urine was quite clear; it had lost the colour so frequently observed in these cases. Thirst may be relieved by lime-water and milk. On account of the pain in the mouth and throat nutrient enemas may be necessary.

Bisulphide of Carbon

In consequence of the solvent influence of bisulphide of carbon upon various resins, such as caoutchouc, or gutta-percha, this substance is largely employed in certain industries. It is a colourless, volatile fluid, with a most penetrating and repulsive odour, and is most destructive to all noxious insect life. Delpech first drew attention to poisoning by carbon bisulphide; and to what he wrote in 1863 little has since been added. His experience was gained in the india-rubber works in Paris, which at that time were very badly ventilated. Carbon bisulphide is used to soften india-rubber so as to allow of its penetration by sulphur in the carrying out of what is known as vulcanisation. During this process the vapour of the bisulphide is inhaled. As a result intoxication follows, and of this there are two stages—(i.) excitation, and (ii.) collapse—an order which resembles that of the intoxication of anæsthetics or alcohol. The illness may be sudden or delayed; the symptoms are headache, cramp-like pains, epileptiform seizures, muscular tremors, imperfect vision or amaurosis, and faintness. There may be great mental excitement or depression. Women suffer from menorrhagia, and if pregnant they miscarry. In the early stages of the intoxication there is sexual excitement; but in chronic poisoning this abates, for in men atrophy of the testes ensues, and in women sterility. The symptoms occasionally resemble those of general paralysis, acute mania, or alcoholism. J. Ross of Manchester observed paralysis analogous to that met with in plumbism; a condition regarded by him as due to peripheral neuritis, marked by a gait not unlike that of locomotor ataxia and accompanied by absence of the knee-jerk. In some respects the neuritis resembled that of alcoholic poisoning; but the muscles were not hyperæsthetic, and loss of colour-vision and amblyopia were present, due, as Mr. Simeon Snell believes, to optic neuritis. De Schweinitz maintains that it is a toxic amblyopia similar to that caused by tobacco. One-third of the patients regain their sight. Ross reported the case of a worker in an india-rubber factory, who complained that the smell of the bisulphide of carbon was always with him, in his food, and in his home; and on leaving work in the evening he would walk like a drunken man and talk a good deal of nonsense. In the following morning he would be miserable and feel wretched. He was glad to get back to work, as inhalation of the vapour seemed to act as a stimulant and bring relief

The muscles of his hands, forearms, and legs wasted; his grasp became feeble, and numbness and tingling of the hands and feet were complained of. "Steppage" gait and double "foot-drop" were present; the knee-jerks and plantar reflexes were absent, but the other cutaneous reflexes were normal.

In my own experiments upon animals bisulphide of carbon was found to be a very deadly poison. It is an anæsthetic, even more rapid in its operation than chloroform, and as profound in its effects. Inhalation of the vapour for a short time by a rabbit was followed by signs of intense excitement. When placed on its feet the animal seemed to be intoxicated, kept swaying from side to side, and then, as if seized by some sudden impulse, bounded forward heedless of objects in its path. When the inhalation was pushed further, not only was there profound sleep with deep stertor, but on regaining consciousness the hind limbs of the animal were paralysed; and so they remained for more than an hour. When rabbits were exposed for a long time to the vapour of bisulphide of carbon, which entered their hutches from an adjoining chamber, they quickly succumbed; one in three days and another in twenty-one. They lost flesh, became tremulous, were easily fatigued, became paralysed in their hind limbs, and died convulsed. All through the period of inhaling the bisulphide the renal function was excessive; and the urine at death, whilst free from albumin and almost completely wanting in urea, contained a very large quantity of sugar. The large cells in the motor areas of the brain were found after death, on staining by Golgi's method, to have their axis-cylinders distorted and varicose; and the cytoplasm of the cell took on staining unequally. Sections of brain stained by Nissl's method, however, did not exhibit this peculiar change. Dogs were readily anæsthetised by carbon bisulphide. It seemed to be a fairly safe anæsthetic, but apart from its extremely disagreeable odour, it produced too much muscular jactation to be a desirable substitute for chloroform. The red blood-cells, whether in dogs or rabbits, did not exhibit any disintegration; and, contrary to the statement of other writers, the blood on spectroscopic examination shewed no trace of methæmoglobin, but only of oxy-hæmoglobin.

I have described the results of these experiments upon animals because they correspond so closely to those exhibited by man. In my visits to the various india-rubber factories of the country, I have become sensible of the enormous amount of suffering which vulcanisation of rubber goods by the "wet" method inflicts upon the work-people. I saw several men who for months had been paralysed in their arms and legs. Many girls had suffered from incomplete loss of power in their hands and legs, headache, vomiting, and extreme drowsiness: so that on reaching home on an evening they would fall sound asleep on sitting down for a few minutes. Many felt so dizzy, and so frequently lost control of their legs, that they staggered as if intoxicated, and occasionally fell on their way home from the factory. Their sleep at night was heavy and unrefreshing. When the weather is hot and close

the work-people suffer most. In one factory brought under my notice three cases of acute mania have occurred; in each case the sufferer was driven by some sudden impulse to throw himself from the top story of the building. Peterson of New York reports a similar result, namely, violent destructive mania. Charcot drew attention to the hysterical character of some of the symptoms; for example, hemianæsthesia with hyperæsthetic patches. The acute stage, however, must be simply regarded as an intoxication.

In an acute case of poisoning, where two ounces of the bisulphide were swallowed without a fatal result, there were pallor of the face, dilated pupils, frequent small pulse, low temperature, and an odour of the poison in the breath. Passing the expired air through an alcoholic solution of triethyl-phosphine produced a red colour. The symptoms resemble those caused by alcohol, and especially those of delirium tremens. Bisulphide of carbon is a strong toxic agent capable, like lead and arsenic, of producing paralysis from polyneuritis. Faradic irritability of the muscles is generally diminished, and frequently the sense of taste is lost.

The treatment consists in the removal of the patient from his work, placing him in good hygienic surroundings, and allaying all excitement by means of rest. Good food, massage and galvanism, with tonics as aids to digestion, are required when nerve symptoms are present.

Nitro- and Dinitro-Benzol and Aniline Poisoning

Within recent years, owing to the impetus given to the manufacture of aniline dyes, numerous cases of poisoning by nitro- and dinitro-benzol have been reported in this country, in Germany, and in the United States. Nitro-benzol is largely employed in perfumery, and is known as the essence of mirbane or artificial almond scent. In cheap confectionery it is used as a substitute for the essential oil of bitter almonds. Its principal use, however, is in the manufacture of aniline, and in the preparation of the explosives known as roburite and sicareit; in the manufacture of these substances the vapour of nitro-benzol is inhaled, or particles of its dust become deposited upon the skin. Benzol is a coal-tar product, and when treated at a moderate temperature with nitric and sulphuric acid it becomes nitro-benzol; treated further at a higher temperature it becomes dinitro-benzol. Some of the injurious consequences of dinitro-benzol are attributed to the presence of impurities; but it is generally admitted that dinitro-benzol itself acts as a poison, whether it be ingested, absorbed by the skin, or inhaled by the lung in the form of vapour or dust. The recent contributors to the literature of nitro-benzol poisoning are Dr. Prosser White of Wigan, Dr. Reynolds, and Mr. Simeon Snell.

Nitro-benzol poisoning is purely an industrial accident. The men who breathe the vapour, and who are said to suffer more than those

who have swallowed it, are sometimes suddenly seized with alarming symptoms. They become extremely sleepy, complain of severe throbbing headache, and occasionally vomit. To these symptoms may be added dyspnœa, dilated pupils, cardiac irregularity, loss of voluntary power, ataxia, and extreme cyanosis. The urine is reddish-brown in colour, and from it and the breath the odour of bitter almonds is exhaled. The patient rapidly passes into a state of coma with symptoms of apoplexy, death being preceded by Cheyne-Stokes respiration. The skin and tongue are discoloured dark blue, probably from the presence of aniline. Such are the symptoms of acute cases of nitro-benzol poisoning. The blood is of a dark chocolate colour, and has lost its power of absorbing oxygen. According to Starkow and Filehne it gives a spectrum similar to that given by acid hæmatin; namely, one absorption band in the yellow between C and D, two between the lines D and E, and a further band to the right. Methæmoglobin gives a similar spectrum. It is interesting to know that blood mixed with dinitrobenzol outside the body does not give these bands except after long exposure to the air and heating.

Death from nitro-benzol poisoning has generally been preceded by coma, although convulsions have been observed. After death the skin is found pale or blue; the brain is congested; the blood all through the body is thick, dark, and fluid; the cavities of the heart are dilated, and the lungs dark or very pale. From the stomach and other internal organs a strong smell of bitter almonds is emitted.

Fifteen drops of nitro-benzol may prove fatal. The rapidity with which symptoms appear after swallowing the poison is greatly determined by the state of the stomach. When large quantities of vapour have been inhaled the symptoms may appear within a very short time—from twenty-five minutes to two hours; and death may follow within a few days. If injected into the veins, the poison, according to Filehne, is almost as rapidly fatal as prussic acid.

In acute poisoning the diagnosis is made from the history, the symptoms, the physical signs, and the peculiar odour of bitter almonds. The principal difference between nitro-benzol and prussic acid poisoning is that the symptoms of the latter are immediately manifested; whilst in nitro-benzol poisoning they are latent or delayed for hours. Should the poison have gained access by the stomach this organ should be washed out. Sinapisms should be applied to the chest and friction made upon the limbs. Stimulants, such as ammonia, or injections of camphor, are called for. Artificial respiration and the application of the faradic current may be necessary to rouse up the patient.

In the less acute cases so fully described by Dr. Prosser White the skin is generally of a dirty yellow colour. There is great languor and loss of weight, and the tendency to sleep is very marked. Men who are thus suffering find it almost impossible to keep awake; yet although they sleep soundly at night, they awake unrefreshed in the morning, generally with severe headache, occasionally with giddiness, and with

almost complete loss of appetite for breakfast. The temperature is often one degree above the normal, the breathing is quickened, precordial and muscular pains and feebleness are complained of. Fatigue is easily induced. The movements become ataxic, and are aggravated on closing the eyes. Tingling and a sense of numbness are complained of in the fingers, hands, and feet; there is hyperæsthesia, which in certain areas is extremely marked, or there is partial hemianæsthesia. The reflexes may be increased or diminished, usually the latter. The muscles react to faradism, but they vary in their sensitiveness to the current. One of the most characteristic signs of nitro-benzol poisoning is a dark maroon colour of the urine. Although like port wine in colour it contains no blood. If the urine, which is acid, be gently warmed, the odour of bitter almonds is readily obtained. The deep colour of the urine depends upon the presence of aniline, nitro-aniline, or some coloured product due to the reduction of the nitro-benzol. The bile pigments in the urine are increased. Patients thus ill usually throw off an excess of urea. The blood is generally of a chocolate colour, and is poor in red corpuscles, which are diminished in size and deficient in hæmoglobin. The blood contains an excess of carbon dioxide, which may partly explain the dyspnœa and cyanosis. In poisoning by aniline cyanosis occurs, a circumstance which, with other data, favours the presumption that nitro-benzol is changed by oxidation and reduction in the body into aniline or possibly hydrocyanic acid, and dinitro-benzol into one or more of the phenyl-diamine series, which are more toxic, also that the symptoms of poisoning are due to aniline. We are still ignorant of the nature of the chemical changes which nitro-benzol undergoes in the body; but it would appear that it may form picric acid in the blood, to which substance the yellow colour of the skin and of the mucous membrane of the intestinal tract has been ascribed by Eulenberg. The substances belonging to this group act as poisons to the medulla oblongata and other portions of the central nervous system, producing peripheral neuritis, and symptoms similar to those of locomotor ataxia and disseminated sclerosis. According to Sir Lauder Brunton they have a direct influence upon muscle-fibre itself. Nitro-benzol rapidly affects the brain, judging from the lethargy and drowsiness so frequently exhibited, and coma. Recovery is possible even when consciousness has been lost for days; but the greatest care must be exercised, as, some time after recovery had apparently taken place, sudden death has occurred in lifting the patient. To Mr. Simeon Snell we are indebted for an account of the amblyopia in dinitro-benzol poisoning. There is often failure of sight to a considerable degree, which is generally equal in both eyes; there is concentric contraction of the visual field with, in many cases, a central colour scotoma, enlargement of the retinal veins, slight blurring of the disc, and pallor of its surface. Mr. Snell believes that the enlargement of the retinal veins is due to vasomotor paralysis.

It is absolutely necessary in factories where nitro-benzol is manu-

factured that only men with robust constitutions should be employed; that the rooms they work in should be well-ventilated, and the temperature not high (for Dr. Prosser White has shewn that a low temperature is always accompanied by a decrease in the sick-rate); that respirators and special clothing should be worn; personal cleanliness observed; the use of alcohol forbidden, and, above all, that the hours of labour should not be long. From the rapid emaciation of the men, and the excessive elimination of urea, it would appear as if the metabolism of the tissues was extremely active; hence the necessity that workers in nitro-benzol should be well fed upon animal food, and that employers should provide them with milk when in the factory.

There is no known antidote to these poisons. If swallowed, the stomach-tube should be used and this viscus thoroughly washed out. Oils, fats and alcohol are contra-indicated. Faradism and sinapisms may be applied as mentioned in an earlier paragraph. Special rules have been framed for the protection of the health of workers in nitro-benzol factories by Dr. Dupré and Sir Hamilton Freer-Smith.

Aniline.—Aniline, of which mention has frequently been made in this section, is obtained from coal-tar oil or naphtha. It is the first substance formed during the process of manufacture of benzol, or benzene. This is subsequently converted into nitro-benzol, from which aniline oil is obtained, the source of magenta dyes. Aniline is a narcotic poison, acting upon the central nervous system, causing insensibility, convulsions, and motor paralysis. Workmen in the factories complain of vertigo, stupor, muscular spasms, deranged sensibility, headache, and cutaneous ulcers. They become chloro-anæmic and suffer from constipation. Several of them complain of being impotent. Aniline destroys red blood-corpuscles and forms methæmoglobin. The urine is generally discoloured brown, or brownish-black. The skin is faintly blue and occasionally the seat of an eruption. In dyeing by what is called the use of "fast blacks," obtained from aniline oil and alkaline bichromates, the workmen engaged in some of the departments suffer, in addition to the symptoms mentioned above, from papular eruptions, ulcers, and scars due to the action of the chrome compounds. The roots of the nails become affected and the skin between the fingers ulcerates. Although in aniline-black dyers this ulceration is less extensive than that observed in bichromate workers, it may yet extend to the bone and lead to loss of the nails and deformity of the fingers.

In France a few fatal cases of acute aniline poisoning have occurred, mostly in children, due to the use of a "patent" for staining boots and shoes. All at once there develop the most marked cyanosis, extreme difficulty of breathing, and signs of cardio-pulmonary distress. Occasionally the symptoms suddenly come on when the patients are out of doors.

Few fatal cases of aniline poisoning have been recorded. In Dr. F. J. Smith's case the patient, a woman aged forty-two, had swallowed three ounces of marking-ink, of which aniline was the principal ingredient.

Shortly afterwards she became unconscious, and remained thus until she died twelve hours after taking the poison; the symptoms and physical signs were purple lips, pale and bluish skin, small pupils, stertorous breathing, and full and slow pulse. The stomach was washed out, ether injected, and oxygen administered; but without avail. The blood is so changed by the action of aniline that it fails to take up oxygen. At the autopsy the lungs were found congested, and the heart relaxed and empty of blood. What quantity of aniline will prove fatal it is difficult to say. Anything over $1\frac{1}{2}$ drachms would probably cause death; although recovery has taken place under treatment after $2\frac{1}{2}$ drachms have been swallowed. For the protection of workers in anilines and aniline dyes the Home Office has drawn out special rules.

Explosives

The dangers incidental to their manufacture and their use in coal-mines—Roburite, Tonite, Melinite, Dynamite, Nitro-glycerin, and Gun-powder.

Since the "Explosives Act" 1875 came into operation, the growth of the trade of explosives in this country and in our colonies has been remarkable, owing to the introduction of smokeless powder and the increasing number of nitro-glycerin compounds that are being placed upon the market. The Government Report for 1899 shews that 11,098 people are employed in their manufacture, and that whilst during that year 54 accidents had occurred, causing 3 deaths and injuring 24 people, most of the accidents happened under conditions to which the controlling provisions of the Act did not apply.

In the manufacture of high explosives *dinitro-benzol* is largely used. The dinitro-benzol is first ground in an apparatus not unlike an ordinary mortar. During this process a considerable quantity of dust is given off, and the atmosphere readily becomes impregnated with the smell of bitter almonds. The yellow powder thus obtained is taken to the mixing-shed, where it is mixed with oxidising salts and heated. Subsequently when cool it is removed. It is at this stage of the manufacture that work-men are specially exposed to the vapours—the dangerous effects of which may be considerably lessened by the use of a fan. Next the explosive is taken to the cartridge-room, where women and girls are employed in filling cartridges. When these are filled they are taken to the dipping-shed, and rendered waterproof by being immersed in liquid paraffin and wax. The men who work in the "grinding" and "mixing" depart-ments suffer from the effects of the noxious fumes; and in the cartridge department, where women and girls are employed, considerable risk to health is run, probably from handling the goods. Of the three varieties of dinitro-benzol which are known to chemists, only one is used in the manufacture of explosives, namely, *meta-dinitro-benzol*; this is admitted to be a powerful poison, whether ingested, absorbed through the skin, or inhaled into the lungs as vapour or dust.

As the symptoms met with amongst those who are engaged in the manufacture of explosives are due to dinitro-benzol, the reader is referred to the preceding section for details of these. It is sufficient here to state that there is a dark-blue colour of the skin, breathlessness, unsteadiness of gait, and amblyopia. In this section we are more specially concerned with the symptoms that occur in those whose occupation, such as coal-mining and quarrying, exposes them to the inhalation of smoke arising from the firing of explosives. Coal-miners have complained of the deleterious effects of such explosives as roburite, tonite, dynamite, nitro-glycerin, and gunpowder. Tonite is composed of barium nitrate and gun-cotton in nearly equal proportions; roburite is an intimate mixture of ammonium nitrate and chlorinated dinitro-benzol in the proportion of 7 to 1. In the explosion of both of these substances the products formed are probably—for roburite, carbonic dioxide, nitrogen, water, and hydrochloric acid; for tonite, carbonate of barium, water, nitrogen, and oxygen. Gunpowder, on the other hand, is an intimate mixture of charcoal, sulphur, and nitre, and the products of its explosion are principally carbon dioxide and monoxide, nitrogen, and sulphuretted hydrogen.

In poisoning by *roburite*, miners, after a prolonged and repeated exposure to the smoke arising from the firing of the explosive, complain of headache, frontal or occipital, dizziness, nausea, and vomiting, constriction at the chest, fleeting pains in the trunk and limbs, numbness of fingers and toes—as if they were asleep, shortness of breath and palpitation on exertion, and loss of vision. To these may be added emaciation and drowsiness. The urine is deeply coloured like port wine. The lips are cyanosed, the face pale, the extremities cold, the grasp of the hand feeble, and there is slight loss of the power of apposing the thumb to the fingers. There is loss of power in the feet, so that the patient cannot stand or walk as formerly. The knee-jerk may be exaggerated or absent; there are also loss of sexual desire, recurrent attacks of dimness of vision, and hyperæsthesia of the skin. Many of these symptoms are attributed to the improper handling of the cartridges by the men; but it has been shewn that in many instances this was never done by miners who suffered; their illness, therefore, could only have been due to inhalation of the smoke in the mine. That the smoke is deleterious to coal-miners has long been believed amongst themselves; it formed the subject of a special investigation both in Northumberland and Lancashire. Ross alluded to the marked anæmia and the blue lips of men, otherwise healthy, who have been exposed to the fumes of roburite—physical signs which indicate that destruction of hæmoglobin has taken place within the blood-vessels; also to the muscular weakness, tingling of the limbs and sluggish patellar tendon reactions, as suggesting the early stage of peripheral neuritis: he therefore regarded the employment of roburite as harmful to the health of the miners. In Lancashire the subject was investigated by a special committee, and the opinion arrived at was that when care was taken to have the shot fired properly, with free ventilation so that the fumes

could speedily escape, the use of roburite was not harmful to the coal-miners. Moreover, it was maintained that in complete combustion of the explosive no trace of nitro-benzene derivatives are left. The coal-miners of the North of England having also objected to the use of roburite, the Durham Miners' Association undertook to solve the question whether the fumes produced from the use of roburite and tonite are injurious to health. The experiments were conducted in coal-mines; the explosives used being roburite, tonite, and gunpowder. By means of aspirators Prof. Bedson removed air from the mines shortly after the shots were fired, and the result of his analyses shewed the absence of deleterious gases in roburite smoke, and likewise in that from tonite. What struck Prof. Bedson in the fumes from gunpowder was their marked visibility compared to those of the higher explosives, and the distinct evidence of sulphuretted hydrogen. In some of the experiments where roburite had been fired there was a distinct odour of nitro-benzene in the atmosphere, although none was found chemically. The injurious substances present in the fumes from these explosives are carbon monoxide, nitric oxide, and sulphuretted hydrogen. The first of these compounds is produced by each of the explosives; and is generated both by the burning of the fuse and by the heated carbonic acid gas passing over the coal, whilst the sulphuretted hydrogen comes from the gunpowder alone. If carbonic acid be taken as a measure of the vitiation of the atmosphere, gunpowder and roburite have practically the same effect; whilst the vitiation from tonite is greater. Gunpowder smoke contains in addition carbon monoxide and sulphuretted hydrogen, both of which are injurious gases. As for carbon monoxide, tonite produces the most, gunpowder comes next, and roburite produces the least. The solution of the problem, so far as the use of these explosives in coal-mines is concerned, is in ventilation and perfect detonation. One of the dangers of these high explosives is that the fumes are invisible; and thus a coal-miner might return to the particular part of the "working" sooner than he would if gunpowder had been used, the fumes from which are visible, in which more solid matter is suspended, and the odour of which is characteristic. The symptoms complained of by the Durham miners, and attributed by them to the firing of roburite, were those of "biliary derangement." Jaundice was occasionally present, and headache, vomiting, and drowsiness; but it did not appear that these symptoms were necessarily due to the use of the explosives, as the nitro-benzene vapours seemed to be present in too small a quantity to be injurious. Besides, many of the symptoms might just as properly be attributed to the ordinary conditions under which coal-miners work, namely, in confined spaces, the air of which is fouled by carbon monoxide, consequent upon the firing of all kinds of explosives. The committee were particularly struck in this inquiry by the rapidity with which the symptoms complained of by the men disappeared. They were much milder, too, thanks to the excellent ventilation of the Durham coal-mines, than the symptoms observed by Ross amongst the Lancashire pitmen.

In all circumstances where these explosives are used it is advised that the fuse should be fired by electricity, and that miners should not return to that part of the pit until at least five minutes afterwards.

Nitro-glycerin, Gun-cotton, Dynamite, Blasting Gelatin, etc.

The history of modern blasting agents can be briefly told. In 1847 Sobrero, an Italian, discovered the sweet viscous substance known as nitro-glycerin. About this time, Schönbein of Bâle, and Baron Lenck, an Austrian, simultaneously discovered gun-cotton. The opinion held by chemists that gun-cotton could only be exploded by detonation, and never by spontaneous ignition, was rudely shaken by the accidental firing of gun-cotton at the Stowmarket factory in 1871. It is the dangerous liability to spontaneous decomposition from heat which has removed this explosive from competition with others of the nitro-glycerin group. As nitro-glycerin under certain conditions is also liable to undergo spontaneous decomposition, Alfred Nobel, a Swedish engineer, sought for an absorbent capable of imbibing sufficient of the explosive to allow of nitro-glycerin still remaining available for blasting purposes, but yet less likely to undergo spontaneous decomposition; of becoming, in fact, a comparatively harmless solid. In certain parts of Hanover Nobel found a porous siliceous earth, of low specific gravity, known as "Kieselguhr," composed of the remains of infusoria. Importing this "Kieselguhr" into the manufacture of nitro-glycerin he invented what is known as *dynamite*; a much safer article for transportation than nitro-glycerin, and much more manageable as an explosive. To explode dynamite heat and strong percussion are necessary. Although a superior and safer explosive than nitro-glycerin Nobel did not rest satisfied with dynamite. For the "Kieselguhr," which he regarded as a weakening element, he substituted nitro-cotton, itself an explosive, and blending this with nitro-glycerin he obtained *blasting gelatin.* This latest explosive of Nobel's, blasting gelatin, is regarded as one of the "cheapest, strongest, and safest blasting agents known to chemistry."

Nitro-glycerin produces peculiar effects upon those who manufacture it. Dr. Dupré, analyst of explosives to the Home Office, informs me that, unlike dinitro-benzol, the effect is transitory; apparently bad effects are never left behind, or very rarely. The work-people suffer at first; but they soon become accustomed to the vapour without any impairment of health. If, however, they leave off work for a time, and again return to the factory, they invariably suffer as at first. In nitro-glycerin factories the men and women do not work on Saturday, as the last day of the week is employed for cleaning up; on resuming work on the Monday a large proportion of the workers invariably suffer for a few hours, the symptoms being extremely severe headache, accompanied by violent sickness and a prostration so extreme as sometimes to require the use of stimulants. Like amyl-nitrite, nitro-glycerin dilates the blood-vessels. Major Cooper Key, H.M. Inspector of Explosives, tells me that

the usual remedies for the nitro-glycerin headaches of workers are a cup of strong coffee and the application of a hot linseed poultice to the nape of the neck. When nitro-glycerin preparations are properly detonated or exploded, the products are practically harmless; they are chiefly carbonic acid, water, and nitrogen. If, however, detonation be imperfect, or if the explosive merely burns, the gases evolved contain much nitrous acid, some carbon monoxide, and perhaps other deleterious compounds. These products of incomplete detonation, particularly nitric oxide, are highly dangerous; and a number of fatal accidents due to them have already occurred in this country and in Australia. Inflammation of the lungs is apt to follow. This develops insidiously, but is extremely fatal. Within a few hours the patient seems as if he had been precipitated into the last stages of pneumonia. When symptoms arise on the inhalation of nitric fumes stimulants and rest in the recumbent position are called for.

To the use of other well-known explosives miners have objected as in the cases of roburite and tonite. Arlidge quoted the case of a boy who inhaled for five minutes large quantities of the smoke slowly evolved from incompletely ignited *dynamite*. The fumes were pungent and suffocating. The symptoms were vomiting and headache, followed by urgent dyspnœa and cyanosis; the patient died twenty-one hours after the exposure. Beyond pulmonary œdema and deep-blue coloration of the bronchial mucous membrane, with punctiform hæmorrhages, nothing was detected at the autopsy. In another patient the symptoms, which arose on the day following the exposure, were semi-consciousness, very rapid pulse, quick breathing—the respirations reaching 96 in the minute—and the physical signs of congested lungs. The temperature was normal. Under the influence of rest, purging and sweating, recovery took place in four days.

The symptoms following the use of *sicareit* (*sécurité*, or *Sicherheit*) resemble those which are caused by roburite; namely, headache, lassitude, cyanosis, rapid pulse, and the emission of deep-brown urine.

The effects of dynamite are a sensation as if the head would burst, difficult breathing, and momentary unconsciousness; symptoms which rapidly disappear on exposure of the patient in the open air.

Picric acid is an essential constituent of several of the high explosives, such as melinite, a secret explosive belonging to the French Government; and it is to the picric acid which it contains that the unpleasant symptoms caused by its use are attributed. In the manufacture of it nitric acid is poured upon phenol, and during the process fumes of nitrous acid are given off along with picric acid which, in its nascent state, causes dyspnœa, dry hacking cough, anæmia, and debility. The vapour stains yellow the conjunctivæ, skin, and hair; and causes conjunctivitis. The dyspnœa tends to become paroxysmal, and the cough may be followed by hæmoptysis. The nervous system and the other internal organs appear to escape. Melinite has not been used to any extent in coal-mining, if at all.

During the South African War much was said about lyddite, and very extravagant statements were made as to what this explosive was capable of accomplishing. The yellow green fumes evolved were believed to be poisonous. Lyddite is stated to be an excellent burster of shells. It is composed of phenol and concentrated sulphuric acid treated with strong nitric acid, the picric acid crystallising out. The fumes of lyddite contain a large proportion of carbon monoxide and a considerable quantity of free carbon, as is evidenced by the black smoke arising on detonation. A yellow deposit forms when detonation is incomplete. "This deposit mingling with the black smoke, tinged with the blue-grey of the pulverised rock, may possibly have given rise to the 'green fumes' which were, according to eye-witnesses, a marked feature at Paardeberg and elsewhere . . . but it is difficult to believe that even in the most favourable circumstances the atmosphere could be rendered unfit to breathe by the bursting of lyddite shells" (A. Cooper Key).

Erb found that in rabbits 8 grains of picric acid produced a fall of the body temperature, diarrhœa, collapse, and death, preceded by convulsions. Most of the tissues were stained yellowish-red. The blood of animals thus poisoned was dirty brown in colour, and the white blood-cells were increased in number. An urticarial eruption, resembling measles, is said to have been caused in men by picrate of ammonia. The urine becomes yellow, and there is a similar discoloration of the conjunctivæ and skin. If the dose be large, vomiting and purging occur.

The symptoms complained of by miners after the use of any of the above explosives may be summarised as headache, giddiness, derangement of the respiratory function, tachycardia, and muscular debility.

Carbonic Oxide (Coal-Gas and Water-Gas) Poisoning

Carbon monoxide, CO, is a colourless, odourless, and tasteless gas, rarely found pure outside the chemical laboratory; it is usually found mixed with other gases. It owes its extremely poisonous character to the fact that, when inspired, it enters into direct combination with the hæmoglobin of the blood, imparting to that fluid a bright cherry-red colour. CO forms so staple a compound with the colouring matter of the red blood-cells that they become incapable of carrying oxygen to the tissues. Thus is it that carbon monoxide is more dangerous than carbon dioxide. Carbonic oxide is present in the fumes emitted from charcoal stoves in which the combustion of the carbon is incomplete. It is one of the products of the combustion of coal, and is the gas which is seen burning with a blue flame in an ordinary open fire. It is one of the constituents of illuminating gas, and it is also present in the fumes escaping from coke ovens; tramps, who have sought the warm shelter of these ovens and lain down beside them overnight, may inhale the fumes and fall into a heavy comatose sleep which occasionally ends in death. In France the fumes from charcoal stoves are frequently inhaled as a

painless means of suicide. The fumes from these stoves are toxic in proportion to the amount of carbon monoxide they contain. Poisoning by carbonic oxide has been frequently confounded with that caused by carbon dioxide (carbonic acid). In the case of carbonic oxide the symptoms are those of a narcotic; the nervous system is gradually lulled into a sleep which ends in coma: whereas in carbonic acid poisoning there is usually greater disturbance of the respiration.

Inhalation of air containing 1 to 2 per cent of carbonic oxide may cause not only unpleasant but very serious symptoms; and whilst the breathing of air loaded with a similar percentage of carbonic acid cannot be accomplished with impunity, the evidence is in favour of carbonic oxide being the more toxic; for life may still go on for a short time in an atmosphere containing 10 to 20 per cent of carbon dioxide. The rapidity with which carbon monoxide unites with hæmoglobin, and the stability of the carboxyhæmoglobin formed, render it a peculiarly dangerous gas. Although in these circumstances the blood has a bright cherry-red colour, it is quite incapable either of carrying or imparting oxygen to the tissues, and thus, internal respiration becoming impossible, the patient dies asphyxiated. When the blood in such a case is examined spectroscopically it shews two absorption-bands between the D and E lines, that is, the yellow and the green. The spectrum is not unlike that given by oxyhæmoglobin, only the broad band is slightly nearer the violet end of the spectrum. Carboxyhæmoglobin is distinguished from oxyhæmoglobin in not being reduced by ammonium sulphide solution. Katayama, too, has demonstrated that whilst the addition of acetic acid and ammonium sulphide (with sulphur in solution) to normal blood produces a greenish-grey or reddish green-grey colour, when they are added to CO blood a beautiful clear rose-red is produced.

Illuminating gas owes its toxic properties to the 5-10 per cent of carbon monoxide it contains; but in "water-gas," which is prepared by acting upon burning charcoal with steam, there is frequently as much as from 30 to 40 per cent or more of carbonic oxide. Water-gas, used for illuminating and heating purposes, is a mixture of carbonic oxide, carbon dioxide, nitrogen, and hydrogen. As this gas has, practically speaking, no disagreeable odour its presence is less easily detected than ordinary coal-gas. Its very large percentage of carbonic oxide makes it more prompt in its action and more dangerous than ordinary illuminating gas. So serious have been the consequences of the inhalation of "water-gas," that some English public bodies have been obliged to do away with it. As carbonic oxide is odourless and tasteless, an individual may be gradually poisoned with it unawares. The presence of from 4 to 5 per cent of carbonic oxide in atmospheric air is fatal to small animals, and 10 per cent is fatal to man. Ordinary illuminating gas frequently contains from 5 to 10 per cent of carbonic oxide, the breathing of which from a leak in a gas-pipe or a tap left open, say in a bedroom overnight, has proved fatal. So insidious is it in its operation and so narcotising is its action that, if respired during sleep, the

sufferer quietly passes into a state of coma which may be very profound; particularly if the gas has been breathed in small quantities and for a long time.

The *symptoms* vary with the amount of carbonic oxide inhaled. Usually, after experiencing a sense of discomfort with throbbing of the blood-vessels, the patient complains of severe headache, giddiness, and great debility. These may be followed by nausea and vomiting. A drowsy feeling may creep on, gradually leading to insensibility, preceded occasionally by convulsions and ending in delirium or coma. The pulse is full and bounding, respiration is accelerated and laboured, the skin dusky, the lips and extremities blue; and by degrees the patient dies asphyxiated. Should recovery take place convalescence is usually tardy, and its course is frequently interrupted by pulmonary or nervous affections. There may be loss of memory for some time afterwards, the urine may contain albumin or sugar, and the lungs be the seat of bronchitis or a low form of pneumonia. Dr. Scott reports the case of a man who suffered from dementia consequent upon carbon monoxide poisoning. Whilst engaged in the ammonia works connected with the blast furnaces of the Clyde Ironworks the man was found lying in front of one of the flues apparently dead. His face was ghastly pale, pupils dilated, breathing shallow and quick, pulse fairly strong but slow: he was completely insensible; but by degrees he became conscious, yet not until after several convulsions. Subsequently he became maniacal, and afterwards listless and apathetic. He had inhaled the "clear gas" that comes from the ammonia works, which Dr. Scott found, on analysis, to contain 25 per cent of carbon monoxide. As a result of carbon monoxide poisoning symptoms resembling those observed in general paralysis may be met with. In two patients, blast-furnace men, sent to me by Dr. Stanley Steavenson of Middleton St. George, I found the speech blurred and scanning, the tongue tremulous, the limbs paretic, knee-jerks exaggerated, and the mental state considerably exalted. These men had inhaled gas rich in CO which escaped from the blast-furnaces when charging them. By this gas, in which there is frequently as much as 30 per cent of CO, the men occasionally become "gassed," and are obliged temporarily to retire from the furnaces. One per cent of carbon monoxide causes unpleasant symptoms; but Hempel has shewn that even such a small proportion as 0·06 per cent may have the same effect. Besides its interference with respiratory exchange, death in such small animals as mice seemed accelerated by a fall of temperature consequent upon diminished metabolism and heat-production. Dr. Haldane has demonstrated that in the presence of oxygen carbonic oxide is much less poisonous than it is in air, and that the poisonous action of carbon monoxide is increased by diminishing the oxygen percentage. When the oxygen tension is high the individual is not so dependent upon his red blood-corpuscles for the carriage of oxygen, as a considerable quantity of oxygen may be taken up dissolved in the blood. There is a limit, however, to which the oxygen tension may be raised; for, as

Paul Bert shewed, at a tension slightly under five atmospheres oxygen itself acts as a poison.

After death by carbon monoxide the blood retains its bright cherry colour for a time, and when shaken it forms a froth of a violet colour. The skin and internal organs, as well as any post-mortem hypostases, exhibit a bright red colour. Occasionally the face is pale. The lungs are frequently congested.

As regards *treatment*, immediate removal of the patient from the presence of the gas, and artificial respiration persisted in for hours in order to expel, if possible, the poison from the blood, rhythmic traction of the tongue, inhalation of oxygen, hypodermic injections of strychnine, and the application of the faradic current to the phrenic nerve, are called for; but even with these measures venesection and transfusion of healthy blood may also be necessary.

In colliery explosions, whilst many of the miners are killed by the force of the explosion, many meet their death by inhaling the "after-damp"—a gas which contains varying quantities of carbon monoxide. The proof that this gas has been the cause of death rests on the pink colour of the skin, a reddening of the face and hands—which gives the bodies an extraordinary appearance of life—and the result obtained by spectroscopic examination of the blood. To the collier working in the pit the presence of carbonic acid (CO_2) or "choke damp" is made known by the extinction of his light, and by a slight embarrassment of his breathing; but carbon monoxide gives no such warning. Alike in those who are working in the recesses of the mine, and in rescuers who descend into the pit after an explosion and are brought into contact with "after-damp," there are the same symptoms—drowsiness, extreme debility, and unconsciousness. Since mice are easily killed by carbon monoxide Dr. Haldane has suggested that they should be carried into such underground chambers as are supposed to contain carbonic oxide gas; and as these animals have a respiratory exchange twenty times as rapid as that of man there would be an interval of several minutes (varying from 12 to 40), after death of the mouse, sufficient to allow the miner to escape. When a colliery explosion has occurred it is absolutely necessary to get fresh air as rapidly as possible into the pit; for although miners may have breathed the "after-damp" and been rendered unconscious by it, death may not supervene for an hour or more. Rescue parties should descend, and, in order that they may remain within the limits of safety, they should carry with them mice and cylinders of oxygen. Artificial respiration, inhalation of oxygen, removal of the miners to bank as early as possible, the administration of stimulants, and maintenance of bodily temperature are necessary.

Sulphuretted hydrogen is extremely poisonous. When present even in minute quantities in the atmosphere it is readily recognised by its unpleasant odour, resembling that evolved from rotten eggs. When inhaled in toxic doses the gas causes death through its action upon the respiratory centre. The fatal termination, which comes with

appalling suddenness and is painless, may be preceded by muscular rigidity and convulsive tremors. Occasionally the breathing is deep and gasping, or a cry is uttered, but before the individual is reached life is extinct. Even when the respiratory centre has ceased to act the heart may still continue to beat. I have made autopsies on three men who died suddenly from breathing sulphuretted hydrogen gas while making excavations for a graving dock on the banks of the Tyne. The post-mortem appearances are practically nil. The blood on spectroscopic examination does not give any other bands than those of oxyhæmoglobin, and it is readily reduced by ammonium sulphide. In a series of experiments upon dogs Dr. Bolam and I found that a dog when placed in an atmosphere containing 0·15 per cent of H_2S would in a hundred seconds become rigid, and fall apparently lifeless, breathing having ceased. By means of artificial respiration the life could be restored, but a percentage above 0·2 was extremely fatal. It was found that when defibrinated blood was exposed for five minutes to H_2S, methæmoglobin took the place of oxyhæmoglobin. The reason why the blood of persons poisoned by the gas does not shew the presence of methæmoglobin is that H_2S kills too quickly for the normal pigment to become converted into the abnormal. Men when working in cesspools and the sewers of cities are frequently overpowered by this gas and rapidly killed. They fall as if struck by lightning, and do not always emit a cry. Although in sewer-gas there are poisonous ingredients other than H_2S—for example, carbon monoxide—the spectroscopic examination of the blood does not reveal the presence of CO, a circumstance which shews the extreme toxicity of H_2S. Often when working in the sewers the men are obliged by headache, dizziness, and feeling of illness to come out into the fresh air, and are rapidly revived thereby. Sulphuretted hydrogen causes death suddenly by acting upon the respiratory centre or upon the terminal endings of the vagi in the lungs, or death comes more slowly through coma, in which the blood is found to be dark and its hæmoglobin altered.

No man should be allowed to work alone in any place where there is a suspicion that sulphuretted hydrogen gas is present. If working in a deep well he should have a belt round his waist with rope attached, and on the slightest failure in response to questions or signals he should be brought to the surface by fellow-workmen, and if breathing has ceased, artificial respiration ought at once to be employed. Oxygen should, if possible, be administered, warmth applied externally, and liquor strychninæ injected hypodermically.

Nickel Carbonyl.—In the manufacture of nickel carbonyl from nickel-copper oxide workmen have died presumably from having respired carbon monoxide that had accidentally escaped. Nickel carbonyl is a clear and very volatile fluid; it boils at 43° C. (109·4° F.), and is a deadly poison. In nickel carbonyl poisoning death has sometimes been rapid, or it has supervened after an illness lasting two or three days, the autopsy revealing extensive inflammation of the lungs as in the early stages of

pneumonia. In the minor forms of poisoning the men feel dizzy, their walk is unsteady, there is difficulty of breathing, and a sense of oppression or of pain in the chest. When a few men have become ill in works there has generally been found some escape of carbon monoxide, and it is to this compound rather than to nickel that some writers, notably Dr. F. W. Mott, attribute the cause of death. In one man who had died in such circumstances Dr. Mott found hæmorrhages in the white matter of the brain and cerebellum, degenerated fibres in the corona radiata, and small patches of softening irregularly distributed. Around these latter was a distinct zone of leucocytic invasion. In my own experiments upon rabbits exposed for fifteen minutes to 15 drops of nickel carbonyl in a large bell-jar freely ventilated no effect was immediately apparent. The animal ran about on being taken out of the bell-jar as if none the worse for its experience. On repeating the experiment two days afterwards, the animal, although on its removal from the jar it seemed quite well, soon afterwards became quiet and listless. Within forty-eight hours it was found dead in its hutch, the cause of death being patchy consolidation of its lungs. Albumin was found in its urine, and on microscopical examination of the brain and medulla, courteously made by Dr. Mott at the pathological laboratories of the Committee of the Metropolitan Asylums Board, numerous small hæmorrhages were found. I am informed that 100 c.c. of nickel carbonyl will give off 73·6 litres of carbon monoxide. This circumstance and the post-mortem appearances just mentioned lend considerable weight to the opinion that in nickel carbonyl poisoning the symptoms are due to carbon monoxide. On this point the last word has not yet been spoken. Ferric carbonyl I have found equally poisonous to animal life. The blood gives the spectrum of carbon monoxide.

Lead Poisoning

Of the various forms of metallic poisoning that caused by lead is the commonest and most subtle. In five years ended 1890 there occurred 1822 deaths from accidental poisoning in England and Wales; of these, 541 were due to lead, 17 to arsenic, and 36 to phosphorus; that is to say, 29 per cent of the total cases of deaths from poisoning were due to lead. Between 1901 and 1903 inclusive there occurred in England and Wales, according to data furnished by Dr. John Tatham, 364 deaths from industrial lead poisoning, 264 males and 10 females; there also died from plumbism due to accident or negligence 8 males and 11 females, while from suicidal lead poisoning 1 female died.

Lead poisoning occurs in isolated cases; or it may assume an epidemic character. Mere handling of the metal for a long time, or inhalation of the dust of the various salts of lead, may be followed by symptoms of poisoning. It has been caused by the accidental or criminal adulteration of food and drink. People are not equally affected by it. There is not only an individual idiosyncrasy—some persons being more

susceptible than others—but there is an hereditary disposition to suffer from lead; and to this may be added a sexual idiosyncrasy, as women —particularly young women—fall more easily under the influence of lead than men.

Lead poisoning is not a modern disease; it has been known for centuries. It is described under various names, for example, plumbism, saturnine poisoning, colica Poitou, colica Pictonum, and, lastly, colica pictorum, from the Latin word *pictor*, a painter.

Setting aside for the moment the industrial forms of lead poisoning, that induced by contaminated drinking-water is the most important. All at once large numbers of people may be stricken with symptoms of plumbism. In such epidemics the gathering-ground has frequently been moorland, the water on which, as it trickles through the peaty soil or comes into contact with decaying leaves, takes up humic acid: this acidified water acts upon the lead of the conducting pipe or the cistern and dissolves out some of the metal. Some chemists maintain that this action on the lead pipes is aided by the presence of iron in the water, which gives it an acid reaction and makes it soft. Distilled water acts upon lead, because it is impossible to remove from the water all traces of organic matter. The presence of nitrogenous compounds confers upon water a solvent influence upon lead—the oxidation of the metal being brought about by the oxides of nitrogen, which, in the form of nitrites, act as oxygen-carriers between the air and the lead. When distilled water acts upon lead it produces a solid white compound, the oxyhydrate; but thus acting alone upon lead it cannot give rise to the oxyhydrate, which is a compound molecule requiring one molecule of water and two extra atoms of oxygen. The hydrogen of the water must be displaced either by high temperature or by the lead receiving oxygen; and the most frequent source of the oxygen are nitrogenous compounds in the water in the form of nitrates. If the water is exposed to the air, a small quantity of nitrate is quite sufficient; for the process is one of continued deoxidation of the nitrate by the lead, and of reoxidation by the oxygen from the air. The proof of this series of deoxidations and reoxidations and that the nitrates are the source of the oxygen, is that if lead be placed in water containing a nitrate, the nitrate is rapidly reduced to nitrite. Nitrogen oxides are almost invariably present in water: they arise from the decomposition of organic compounds in which the operation of micro-organisms probably plays an important part. The oxyhydrate of lead, already alluded to, is very insoluble in pure water; but if the least trace of acid be present, or certain salts, such as nitrate of ammonia, it is freely soluble.

Mr. Garrett found, when distilled water has acted upon lead for 84 hours, that it contains $\frac{1}{100}$ grain of metallic lead per gallon; that if one grain of sulphuric acid per gallon were added, in 84 hours it contains $\frac{1}{8}$ of a grain, whilst the same quantity of nitric acid gives $\frac{1}{3}$ of a grain in an equal period. The retention of water in a lead service-pipe overnight may therefore allow of the solution of a fairly large quantity

of the metal—which explains the fact that many of the victims of plumbism have been persons who drank the water first removed from the pipe in the morning. It is thus, too, that barmen and barmaids have suffered by taking regularly the first swill of beer which has been in the tap overnight. A short time suffices for liquids thus to become contaminated. Water kept in contact with a lead pipe for half an hour has been found to contain $\frac{1}{10}$ grain, at the end of an hour $\frac{1}{3}$ of a grain, and at the end of 12 hours 1·4 grain per gallon. The presence of a very minute trace of lead in drinking-water is sufficient to cause serious symptoms. Experience shews that if lead be introduced into the system in very small quantities, and for a long time, it is more likely to cause serious symptoms than when it is taken in larger doses and only on a few occasions. Cases illustrating the poisonous doses of lead are quoted by Dr. De Chaumont (in which the water contained $\frac{1}{20}$ grain per gallon); Dr. Hunter of Pudsey ($\frac{1}{15}$ to $\frac{1}{20}$ grain); Dr. Angus Smith ($\frac{1}{100}$ grain); Dr. Adams ($\frac{1}{100}$ grain); Dr. Sydney Ringer ($\frac{1}{50}$ grain): in one of Dr. Dixon Mann's cases the drinking-water contained 2·4 milligrammes of lead per litre, and in one of my own cases serious symptoms arose from drinking water which contained 0·0028 grain of lead per gallon. Of the family of Louis Philippe, at Claremont, 34 per cent who drank the water, which contained $\frac{7}{10}$ grain per gallon, suffered from plumbism.

During the action of water upon lead the crystalline oxyhydrate of the metal is formed. If certain salts are present in solution there is a transference of portions of the acid radicles to the base, resulting therefore in the formation of salts of lead other than the oxyhydrate. Salts of lead more soluble than the oxyhydrate may thus be formed; for example, nitrate, nitrite, or carbonate. The presence of carbonic acid increases the solvent influence of water upon lead. The oxyhydrate first formed by the water is dissolved by the carbonic acid present, and a considerable quantity of lead may thus pass into solution as acid carbonate; but as the formation of oxyhydrate continues, the carbonic acid is neutralised, and there results a basic carbonate of lead which is insoluble and is deposited upon the surface of the pipe, forming a protective covering whereby further action of the water is at least retarded if not prevented. In these circumstances the addition of alkaline carbonates to water may prevent lead poisoning. Water acts with greater vigour upon a new than upon an old lead pipe; for on the surface of the latter a protective covering of the dehydrated oxide or carbonate may be present: both of these, however, are readily dissolved when the water becomes slightly acid, or when its temperature is raised; hence the danger of using water for culinary purposes first drawn from the kitchen boiler in the early morning. It has been stated as an offset against this danger that if tea be made with water containing a trace of lead the metal is discharged, but experiment has shewn that there is no truth whatever in the statement; moreover, there is the risk that the tea itself may have been contaminated by a wrapper of leaden foil. In one experiment with

water containing $\frac{1}{24}$ grain of lead per gallon, the tea infused from it contained $\frac{1}{23}$ grain.

The drinking-water in our houses should be free from such contamination as we have been considering. Water that naturally contains carbonate of lime is not acted upon by lead; and we have seen that the addition of alkaline carbonates is a preventive: so are alkaline phosphates and silicates. When water has filtered through a bed of sand it is not so liable to be contaminated by lead in its transit through the pipes, as the water takes up a certain amount of silica, which unites with any dissolved lead to form an insoluble silicate, and this forms a coating on the inside of the pipe. To cause plumbism it is not necessary that the drinking-water should contain lead in solution. One of the most serious cases of saturnine poisoning that I have seen in consultation was that of a lady in Kensington, who with one of her sons suffered severely from using water taken from a cistern in which several loose lumps of white lead had been left by a careless workman. The water as it flowed from the cistern was muddy: it contained a large quantity of lead in a precipitated form, but none in solution. Lead had been deposited upon vegetables boiled in this muddy water, and thus it gained an entrance into the system.

When drinking-water contains lead, the addition of sulphuretted hydrogen or ammonium sulphide at once precipitates the metal as a dark brown sulphide—care having been previously taken to add a small quantity of hydrochloric acid to it to precipitate any iron that may be present. Should there be only a minute trace of lead in the water the addition of a small quantity of barium sulphate ($\frac{1}{2}$ grain) allows of the precipitate coming down in two layers: the lower stratum forms rapidly, and is composed of denser particles, whilst the upper, being lighter, takes a longer time to subside; in this the sulphide of lead is deposited. A buff or dark brown colour is thus imparted to it, which causes it to stand out in distinct contrast to the underlying well-defined white layer. By this means $\frac{1}{200}$ grain of lead per gallon may be detected. Occasionally it is necessary to test the "plumbo-solvency" of a suspected water, and for this purpose nothing is better than the "shot" test of Whitelegge, namely, filtering the water through lead shot specially prepared free from arsenic and then testing it.

We have dealt at length with the question of epidemic plumbism, for the disease has rather increased than diminished of late; and it will tend to become even more prevalent as our rapidly growing town-populations go far afield in search of water. Moorland waters, in the late summer and autumn months, are strongly impregnated with peaty acids. Water, according to Mr. Power and Dr. Houston, may simply dissolve lead by a true plumbo-solvent action, or it may possess an "erosive ability," whereby it forms an almost insoluble lead compound so loosely attached to the lead as not to shield it from further attack. Distilled water possesses the first power, moorland water both: and although boiling may destroy the property possessed by distilled water,

moorland waters remain unaffected. It has been demonstrated by Dr. Houston that two kinds of bacteria, probably derived from peat, are present in moorland water, and are capable of generating an acid which imparts to water its power of dissolving lead.

Lead salts are all more or less poisonous. Even so insoluble a salt as the sulphate is acted upon by the intestinal juices, and is more or less soluble. In my own experiments animals that received sulphate of lead died, and the livers contained lead. The sulphide of lead is very insoluble; hence the preventive treatment of plumbism by giving sulphur in milk. Chromate of lead is also very insoluble, and yet it has frequently caused poisoning by diffusion as fine dust through the air in the carding-rooms of woollen or cotton factories, effects which have disappeared at once on the introduction of fan ventilators.

Lead finds its way into our victuals when these are cooked in cheap enamelled or tinned ware, and in the adulteration of articles of diet, for example, flour or pastry coloured yellow by cheap baking powder, wines, beer, and cider, tinned meats, cream of tartar, and tea wrapped in leaden foil. The latter is a source of danger because of the excessive tea-drinking of the labouring classes. It is only right to add that lead has not always been found in tinned jellies and meats, although present in the solder. A cheap solder is sometimes used in France for sardines: it contains 67 per cent of lead and 33 of tin.

It is sometimes extremely difficult to detect the source of plumbism. A short while ago a lady was sent to me from Macclesfield suffering from extreme anæmia, headache, and recurrent colic. As her symptoms always disappeared when she went away from home for a period, the wall-paper of her bedroom was examined, and found to contain lead; so, too, did the patient's urine. After treatment, removal of the wall-paper, and change of the bedroom for a time the patient made a good recovery. Lefour quotes the case of a husband and wife who were similarly affected by a wall-paper which contained 23 grammes of lead per square metre. Out of 11 samples of wall-paper examined 9 contained lead varying from 18 to 119 grammes per square metre.

Industrial lead poisoning claims many victims annually due to the inhalation of dust, the swallowing of impregnated saliva, eating with unwashed hands in the workshop, the adhesion of lead dust to the clothes of the work-people, or to the solution of it in the sweat and absorption by the skin. Improved ventilation of factories, attention to stringent rules of cleanliness, restriction of female labour, medical examination of the work-people on first entering the factory, and afterwards at weekly periods, have done much to diminish industrial plumbism; but the abolition of all hand-work and the substitution for it of electrolysis in the manufacture of lead are highly desirable.

Lead-mining in this country is no longer the extensive industry it was of yore. It is still pursued in some of the dales of Durham, Yorkshire, Cumberland, and the Peak of Derbyshire. Foreign ores, particularly the Australian and Spanish, are richer in silver than ours, so that

at the present time most of the metallic or pig lead used in this country is imported. English lead-ore seldom contains more than eight or ten ounces of silver to the ton; but in Spanish there may be 40 to 80 ounces to the ton. The process of desilverisation cannot be regarded as an unhealthy one to the operative. The silver is extracted by the zinc or Parkes' process, the principle of which is that in smelting the ore zinc alloys itself with silver and floats on the surface.

The British lead-miner runs little or no risk from plumbism. The getting and handling of the ore is unattended by such symptoms as colic, headache, or paralysis; for in Britain the lead in the mines is almost pure metal mixed with spar. In the Broken Hill mines of Australia the ore exists in the form of carbonate; and many of the miners there have died from lead encephalopathy. The lead-miner at home, however, runs other risks. The mines in many instances are deep, damp, and badly ventilated—and the ingress and egress are difficult. The men become prematurely old: they suffer from cough and spit. Many of them die of phthisis, in which the lungs present the characters of fibroid change. In the indurated lung we find no traces of lead, but tubercle bacilli are in the expectoration. Many of the lead-miners also suffer from distorting rheumatoid affections of the joints.

The dangers of plumbism arise during the smelting of the metal; but of late this has been diminished by placing a hood in front of the furnace, and by free ventilation. Nevertheless lead-smelters are pale, and occasionally suffer from colic. But there is a more widely spread danger than that to the smelter. The white fumes that issue from the stack contain large quantities of lead; and, as the lead is deposited on the soil, cattle grazing in the neighbourhood have suffered and died from plumbism, the disease being spoken of as "bellond." Moreover, the flues from the smelting stacks have to be cleaned out from time to time; and the men who enter them for this purpose suffer from severe headache and giddiness. The remelting of old lead is not without danger; and as this is frequently carried on in small shops or private houses, people living in the immediate neighbourhood have shewn symptoms of plumbism, and pregnant women and animals miscarry. In the fumes emitted from the chimneys, lead, zinc, manganese, and arsenic have been found. The melting of old lead pipes is then, in my opinion, much more dangerous than smelting the ore, probably from the large quantity of lead carbonate or organic compounds present. A similar danger attends the breaking up and burning of old railway carriages.

The white-lead factories supply the largest number of cases of plumbism. Lead poisoning also occurs among potters, who dip their ware in glaze, and amongst enamel-plate makers and tinners of cheap hollow ware. Metallic lead is not so dangerous as its salts, and yet the file-cutters of Sheffield who hammer their files upon a lead cushion frequently suffer from plumbism. The more soluble the salt of lead the greater is the danger. White lead or carbonate is the most harmful owing to its extensive employment, and it is on this account that various

substitutes have been tried for it; but for purity, whiteness, and durability on exposure it is still superior to all pigments. White lead is usually made in this country by what is known as the old Dutch process, for the details of which chemical text-books should be consulted.

House-painters suffer from plumbism. In burning off the old paint there is usually considerable stithe; inhalation of which causes colic, vomiting, and severe headache with constipation. This predisposes the individual so far that he readily succumbs to a fresh invasion of the poison. It is not so much the use of the brush and inhalation of the terebinthinated lead vapour that affect house-painters. Several coats of paint, for example, have to be applied. After the processes known as "prime" colouring and "puttying" with white lead comes the "flat" colouring. It is when these coats are dry that the painter, using sand-paper to make the surface flat, creates a cloud of dust, inhalation of which is frequently followed by colic or wrist-drop. Similarly, in paint and colour works it is the dust generated during the grinding and mixing of white lead that is the main cause of plumbism. The men who work in electric accumulator factories, and who fill in the plates with a lead paste, are particularly liable to colic and the severer forms of plumbism. Lead poisoning in these circumstances develops with extreme rapidity.

Lead gains access to the system by the skin, the respiratory passages, and the intestinal tract. It may also enter through the vaginal mucous membrane from the use of lead lotion in douching, and the lacrimal by collyria. Animals whose skin has been smeared with oleate of lead have died; the long-continued application of medicated plasters and the use of cosmetics and hair-dyes containing lead have caused plumbism, also the frequent handling of metallic lead. The metal or its salts in the form of dust may enter by the respiratory channels; the salts, becoming deposited by the alkaline juices of the respiratory passages, are first converted into carbonate and then into the more soluble bicarbonate. When lead has thus gained access symptoms are quickly induced, and they are usually more severe than when the metal has been swallowed. Entering the gastro-intestinal canal, it is acted upon by the gastric juice, the hydrochloric acid of which is sufficient to convert a quantity into soluble chloride. It has been demonstrated that during the simultaneous digestion of proteid a very small quantity of lead only is dissolved. Lead salts are also dissolved by bile, but if bile is allowed to act upon fat at the same time very little of the salt enters into solution. We have found pancreatic juice inactive upon lead. It is the hydrochloric acid of the gastric juice that is the active agent. When, therefore, lead salts have passed out of the stomach along with the acid chyme, there is nothing in the intestine, except bile, likely to act upon them—unless it be the acid products of bacterial life—and as sulphuretted hydrogen is always present in the intestinal canal, there is the probability that an insoluble lead sulphide will be formed, and thus eliminated. Plumbism is more likely to arise where very minute quantities of lead are repeatedly taken into the system than after a few larger doses. Small quantities

are more completely dissolved, are more readily absorbed, and not so freely eliminated.

It is with plumbism as with intoxication in general; certain circumstances intensify the disposition to it: the younger the age the greater the liability, and particularly is this the case with women. Young women who are anæmic and ill-nourished are rapidly brought under the influence of the metal, and in them the nervous system is especially apt to suffer. In one of my own cases a month's work in a white-lead factory proved fatal to a girl. In five years ended June 1889, 135 cases of lead poisoning were admitted into the Newcastle Infirmary: of these 91 were women and 44 men. The susceptibility of women was exhibited from the ages of 18 to 23; the largest number of admissions being at 19 and 22 years of age: the greatest susceptibility of men was from 41 to 48. In a second five years' series of admissions ended June 1894 the largest number of female admissions was at the ages of 19 and 25; and whilst males shewed a tendency to suffer at 26, the larger number occurred after 40 years of age.

The drawing or emptying of "stoves" is regarded as the most dangerous part of white-lead making. Improper feeding, general destitution, and previous illnesses, alcoholic intemperance, and working in a badly ventilated factory, are circumstances which, with menstrual irregularities, strongly dispose young women to lead poisoning. During recent years outbreaks of lead poisoning have occurred in the midland counties among women of the child-bearing age from the ingestion of diachylon as an abortifacient.

Lead poisoning occurs in four forms. In the first colic is the most important symptom; in the second the central nervous system is profoundly affected, the patient being the subject of epileptiform seizures called "lead encephalopathy"; the third is the neuro-muscular form, in which "drop-wrist" is the most marked symptom; and in the fourth are included all those cases of chronic plumbism characterised by profound cachexia, early decrepitude, and albuminuria.

Colic is usually one of the earliest symptoms of lead poisoning, but it is generally preceded by anæmia. One of the earliest indications of plumbism is a peculiar anæmia or cachexia—the face becomes pale, and there is complaint of inability to take food, particularly in the morning, a metallic taste in the mouth, and of sickness, with or without constipation. If these premonitions be disregarded the patient is sooner or later seized with acute abdominal pain, usually paroxysmal. Colic, as a rule, is accompanied by constipation, but not necessarily so. The bowels may be fairly regular, very constipated, or slightly loose. As a rule there is constipation, and that, too, of an obstinate character. Since colic, constipation, and vomiting are usually present together, they constitute the saturnine triad. The abdominal pain may be so severe that the patient cannot allow the abdomen to be touched. In other cases relief is obtained by firmly pressing the abdomen, or by applying warmth externally. The pain of lead colic has a double character: it is superficial

or deep, *i.e.* dermal or muscular. It is the former or paroxysmal pain which is aggravated by pressure, the other is constant and is more of a dull aching. Days after the superficial or paroxysmal pain has subsided deep pressure upon the abdomen elicits signs of suffering, and the peculiarity of this pain, and sometimes too of the colic, is that it is either limited to one side entirely, or is more acutely felt on pressure on one side than the other. Frequently localised near the umbilicus, it may extend as far out as the external border of the rectus muscle; or it may be diffused over the upper half or two-thirds of the abdomen. Accompanying the colic there may be painful micturition, pain in the region of the kidneys or in the testes with retraction of these glands. The muscular walls are generally hard and retracted, but not necessarily so, for the abdomen may be of normal form, or there may even be localised or general distension. One-sided localisation of the pain is notable, and concurrent with it I have frequently noticed that extreme pain is felt when firm pressure is made upon the line of the vagus in the neck, particularly on the corresponding side. It is interesting to note, too, that during recovery the disappearance of the vagus pain in the neck is contemporaneous with that which was elicited by pressure on the abdomen. Moreover, the pupils are generally unequal; the rule, though not an invariable one, being that the pupil on the same side as the abdominal pain is smaller. The radial pulses also are unequal, that on the affected side being stronger or weaker as the case may be. In addition to colic, there is pain in the muscles of the arms or legs. The knee-jerk is usually exaggerated on the affected side. Even when the colic is distributed all over the abdomen the pupils may be unequal; one or both may be dilated, and there may be the inequality of the radial pulse already described.

Constipation generally accompanies the colic, but relief to pain does not immediately follow the action of the bowels. For several days, even though the bowels are being moved by aperients, pain may still be complained of and vomiting may continue. Occasionally diarrhœa is present and persists during the colic. When the colic is severe the patient looks thoroughly ill; the face wears an expression of suffering, he rolls about in agony, and is with difficulty restrained. This peculiar restlessness is characteristic of acute lead colic. The acute abdominal pain may last from three to eight days and then disappear, the cure being complete; but in the chronic form the pains may recur, although with less severity, especially after food or fatigue, and be accompanied by nausea. Usually acute lead colic is unaccompanied by a rise of temperature. When there is feverishness there is a slightly increased pulse-rate proportional to the pyrexia. A rise of temperature with colic suggests the probability of a subacute gastro-enteritis.

It is difficult to explain the colic. Some authors believe that lead acts primarily upon nerve-ganglia; others upon the muscular fibre of the intestinal wall, or upon the musculature of the intestinal arteries. Dr. Haig attributes it to the deposit of an insoluble lead urate, and therefore

administers sodium salicylate. In animals that have died from plumbism I have found the small intestine irregularly contracted; at places so extreme was the spasm that the intestine felt like a piece of cord—its calibre being obliterated. Was the contraction of the intestine in these cases due to the direct action of lead upon the muscular fibre, or had the arteries become contracted primarily, and thus, by shutting off the blood-supply, caused nervous excitation and muscular contraction? Clearly the pain is due to extreme spasm of portions of the intestine and pressure upon sensitive nerves—and the recurrent pain would be explained by the effort of the dilated segments of the intestine to pass on their contents into the constricted portions below. Spasm and arterial ischæmia, by cutting off the supply of liquid, would aggravate constipation. It is probable that the nerve-ganglia are first affected.

Lead Colic and Appendicitis.—In lead colic pain may be referred to either iliac fossa. Considerable difficulty of diagnosis may, therefore, be experienced when pain is complained of in the right ileo-cæcal region. Patients suffering from lead colic have been operated upon for supposed appendicitis which was not present, and operations have not been done when they ought to have been. The difficulty of diagnosis is increased by the fact that a patient who is suffering from lead colic may have appendicitis as well. It is a moot point as to how far lead as a toxic agent may be a cause of appendicitis, since perforating appendicitis followed by death is known to have occurred in plumbism. Appendicitis would thus be a complication of lead colic. The only thing to do in the circumstances is to watch the patient carefully for a few hours. A slow pulse, absence of fever, early vomiting, and a diminished area of hepatic dulness would favour the diagnosis of lead colic as against appendicitis. A diagnosis cannot be made on the situation of the pain alone, for while in lead colic this is usually the umbilical area, the pain may extend beyond this area; it may be, *e.g.*, epigastric or hypogastric, and besides in appendicitis the pain, though usually referred to and aggravated by pressure in the ileo-cæcal region, does not always commence there.

Accompanying the colic we find—(i.) the radial pulse extremely small, almost imperceptible; or it is hard, resistant, and of high tension: (ii.) oliguria—the excretion of urine is reduced to a minimum. The pulse may be as slow as 40 to the minute. In some patients an extremely feeble pulse is characteristic of this period; so feeble is it that even the sphygmograph may fail to register it, and yet during colic there may be heightened arterial blood-pressure which comes and goes with the pain. It is no uncommon thing for colic to disappear and reappear; and this change is accompanied by relaxation and heightening of the arterial pressure. Disappearance of the colic is usually attended by a return of the blood-pressure to the normal. It does not necessarily follow that the high blood-pressure is due to the abdominal pain, for it may persist in the intervals, besides the arterial pressure is not high in other forms of colic. Still in lead colic, intestinal spasm and vaso-constriction in the splanchnic area, which is one of the principal causes of high arterial

pressure, frequently go together. The small amount of urine excreted during colic is noteworthy. It may fall as low as 8 to 12 ounces per diem, and in young subjects, particularly in first attacks, it is free from albumin. Except that it contains too little urea the urine at this stage, although lessened in quantity, presents no special feature. When the colic disappears, not only does the quantity of urine rise, but the urea as well. If saturnine colic be unaccompanied by complications the patients gradually recover, although in the early stages there are apt to be remissions. The mortality in this condition is practically speaking nil.

In plumbism the face is usually pale: in the chronic forms the face is rounded, the features are expressionless, and the *anœmia* passes into a cachexia which may never disappear. On the gums may be observed a bluish-black line along the margins close to the teeth; this is absent, however, if the teeth have fallen out, and in people who have regularly used the tooth-brush. It is frequently associated with ulceration and retraction of the gums, so that the teeth appear elongated and discoloured. Running up between the teeth may be seen small pyramidal masses of gum with well-defined blue margins. First described by Burton, the presence of the *blue line on the gums* is a considerable aid in diagnosis; and yet it may be present for months in the gums of lead-workers who are not suffering from plumbism. Its persistence, however, is an indication of the presence of lead in the system. Other substances besides lead may cause a line on the gums. I have seen a deep black line on the gums of a coal-miner. In people who have been taking bismuth or copper, and whose teeth are decayed, a livid line is occasionally met with; in a child poisoned by tetrachloride of gold Sir T. Stevenson found a purple-black line at the junction of teeth and gums. A delicate blue line is sometimes noticed on the gums of workpeople exposed for a few hours to an atmosphere laden with lead dust; but, as it disappears on rinsing the mouth, it is a deposit of sulphide of lead on the mucous membrane and not in it. The characteristic blue line occurs at the margin of the gum where it is not in complete apposition with the teeth; and it is usually more pronounced on the lower than the upper gum. The presence of bad teeth, ulcerated gums, and want of cleanliness favour its establishment. In a few days after exposure to the poison the line may appear, and it persists. Its disappearance is not perceptibly hastened by friction or by the use of mouth-washes; nor is it quickly removed by medicines. The shortest times in which I have noticed its disappearance are from two weeks to four months. On other portions of the mucous membrane of the mouth bluish-black patches may be observed; a frequent site of them being just inside the lower lip. It has been stated that the administration of potassium iodide in a case of plumbism will bring out the blue line if absent; but we have no proof of this. On microscopical examination of the gum numerous black granules of sulphide of lead are observed in the deeper cells of the epidermis, also in the large phagocytic cells of the connective tissue where ulceration has taken place, and not, as Fagge taught, in the small

blood-vessels. Occasionally the mucous membrane of the lower part of the small intestine or of the ascending colon shews patches of bluish-black staining, and on microscopical examination the deeper cells of the mucosa are found to contain particles of sulphide of lead.

As regards the pallor, which is nearly always present, or the well-marked saturnine cachexia of the older cases, the blood is deficient in red cells without any increase of the white. In plumbism the pallor of the face is often greater than the blood-count explains. The red blood-corpuscles in my own patients have varied from 2,700,000 to 3,500,000 per c.mm., the white corpuscles have averaged 10,000, and frequently the hæmoglobin has been less than 50 per cent of the normal. It would sometimes appear as if the anæmia was proportional to the length of exposure to lead. Mr. Goadby draws attention to the presence of minute basophil granules in the red blood-corpuscles of lead-workers, which with Leishman's stain look bluish-green. Plehn found similar bodies in malaria. André found not only basophil granules in the erythrocytes, but also a few nucleated red blood-corpuscles in a man who had been exposed to lead for only three months. In one of my own patients the blood on microscopical examination was found to contain 3,200,000 red corpuscles per c.mm. and 6875 white, the differential leucocyte-count being—polymorphonuclear, 66 per cent; small lymphocyte, 20 per cent; large lymphocyte, 6 per cent; eosinophil, 8 per cent. The thyroid gland is extremely small, and in old cases there is atrophy and gelatinous degeneration of the marrow of bones. Prof. Stockman and Dr. Charteris examined the bone-marrow of the femora of ten rabbits poisoned by lead, and found that while the fat-cells had disappeared there was an increase of the marrow-cells. The cells that multiply are the leucoblasts, *i.e.* those which give rise to the finely granular polymorphonuclear leucocytes of the blood. It may be that this increased number of leucocytes has for its object the absorption of the poison, since a similar condition is observed in arsenical and other forms of mineral poisoning and in toxæmias. The submaxillary gland may be swollen, also the parotid and sublingual glands. Occasionally the nails exhibit trophic changes. They break readily, are short and notched. In a female lead-worker I found the nails of the hands and feet had a peculiar yellow-brown colour as if they had been painted with weak iodine. Associated with trophic changes in the nails there is usually neuritis.

It may be partly due to anæmia, and to the peculiar effects of lead upon menstruation, that women are more susceptible than men, and at an earlier age. This is not because women are more exposed to the specially dangerous processes in the manufacture of white lead. Menstruation is apt to be increased; but whilst in many cases there is menorrhagia every two or three weeks, in not a few there is amenorrhœa. Some writers attribute the headache, so frequently complained of by female lead-workers, to the scanty menstruation. This may aggravate, but it is not the cause of the headache, for headache is equally a symptom in plumbism where there is menorrhagia. Pregnant women readily abort.

So frequently is the tendency to miscarry exhibited by female lead-workers, that the only means sometimes by which the full term of pregnancy can be reached is to leave the factory altogether. This tendency to miscarry is equally well seen in the lower animals under experimental plumbism. Rabbits readily thus abort. In the lower animals the influence of sex in increasing the susceptibility to plumbism is just as noticeable as in the human female. In the female sex generally, not only is metabolism less active, but excretion is not so well performed: women suffer more from constipation than men, and though they pass relatively as large a quantity of urine as men, it has a lower specific gravity, and is relatively deficient in solids, particularly in urea. The elimination of nitrogen, therefore, is not so perfect as in men, and it is disturbed by the return of each menstrual period. Add to the effects of diminished nitrogenous metabolism and to variations in renal excretion those of constipation and irregular, profuse, or scanty menstruation, and we probably have the explanation of the greater susceptibility of women to lead poisoning than of men.

The nervous system is peculiarly prone to be affected by lead, and the extent to which it is affected is a measure of the menace to life. Colic or wrist-drop usually precedes cerebral symptoms in plumbism; but in many cases the only premonitory symptom is severe headache, during which the *tache cérébrale* may be obtained; and then without further warning the patient is suddenly seized with a fit of varying severity and duration: this passes off, only to be repeated with increasing severity, until the patient passes into a state of coma from which he may never rally. Epileptiform seizures may be the only symptom of plumbism; but in other cases colic, wrist-drop, and fits are present at the same time. To the epileptiform seizures the term "lead encephalopathy" is applied, and of all forms of plumbism this is the most dangerous. It is the most fatal form, and in young women it is frequently preceded by symptoms which appear to be of a hysterical nature. So slight and seemingly functional are these hysterical symptoms that they have frequently thrown careful observers off their guard. Gradually they have deepened and been succeeded by epileptiform seizures, and within two days the patient has died. Debove and Achard applied the term "toxic hysteria" to those cases in which a neurosis arises under the influence of intoxication. Occasionally in plumbism hysterical paralysis is met with, accompanied by hemianæsthesia and amblyopia on the same side and anosmia on the opposite. Yet we do well to remember that saturnine toxic hysteria is frequently the forerunner of a very fatal form of lead poisoning. In lead encephalopathy the fit may only last a few minutes, consciousness being rapidly regained. The patient is usually very restless; there is great excitement, amounting to delirium, or there are dulness and melancholia. In the intervals the pulse is sometimes so feeble as scarcely to be felt; the excretion of urine falls—3 or 4 ounces only in the twenty-four hours—and it may contain albumin. The fits, however, keep recurring, and in one of them the patient dies, or he may

recover; but his vision has become affected to the degree of complete or incomplete blindness; or aphasia may be present.

In the neuro-muscular form the patient, after having experienced pain or numbness in the muscles of the forearm and leg, and perhaps too, but not necessarily, one or two attacks of colic, suddenly or gradually loses the power of his wrists; the hands fall powerless from the wrists, or the arms from the shoulders, and he lies in bed with hands crossed, unable to feed and clothe himself. This is the milder form of lead paralysis, and it affects the extensors mainly. The paralysis is usually bilateral, one side, however, being generally worse than the other. The muscles of the calves are tender to the grasp. There is rapid muscular atrophy. Occasionally the paralysis is widely distributed, the muscles of the trunk, back, and shoulders become affected and are painful on pressure. While wrist-drop is the common form of lead paralysis in the adult, it is not so in children. In them the poison has a greater preference for the lower than the upper extremities—hence ankle-drop with loss of the plantar reflex.

In the fourth form are included the victims of chronic plumbism. They present the history of a long exposure to lead and repeated attacks of colic; possibly, too, of wrist-drop and of one or two epileptic seizures. The patient is extremely cachectic; the metacarpo-phalangeal joints may be swollen, or other joints may be the seat of gout or rheumatism. The extensor muscles of the wrists and fingers may be atrophied. There is general malnutrition; the gums are ulcerated, and probably shew a blue line; the sight is defective; the urine contains albumin; the health gradually fails; the individual is prematurely old, and he dies from some intercurrent disease. At the post-mortem examination the heart, kidneys, liver, and arteries shew pathological changes.

Paralysis is usually regarded as a symptom of *chronic* plumbism; but it may occur in the *acute* form without being preceded either by colic or headache. The loss of power precedes the atrophy; when wasting once begins it advances rapidly. Paralysis of the extensor muscles of the wrists causes "wrist-drop," but it is noticed that the extensors of the fingers are also similarly affected—not all equally, however; the index-finger, for example, may not be so deeply paralysed, and consequently it recovers more quickly than the others. The flexors of the fingers, too, generally become paretic; so that when any effort is made to extend the fingers the flexors imperfectly contract and are thrown into a state of tremor. The supinator longus as a rule escapes; but if the muscles of the upper arm become affected this muscle is not exempted: supination of the hand is accomplished by an external rotation movement of the shoulder and a throwing-out of the hand by the patient. The index-finger may be affected, whilst the little finger escapes; or the thumb may not be so easily extended, its abductor and adductor muscles being paralysed; the fingers probably cannot be separated; the interosseous grooves deepen, and the back of the forearm becomes flattened in the muscular atrophy.

Whilst lead has a strong predilection for the nerves supplying the

muscles already mentioned, these may escape, and those of the upper arm be attacked; namely, the Duchenne-Erb group—the deltoid, biceps, brachialis anticus, and supinator longus. To this group is generally superadded paralysis of the supra- and infra-spinati. This form of paralysis is usually bilateral, and occurs in the more inveterate types of lead poisoning. Of this group of muscles sometimes the deltoid is the only muscle affected, as in a case reported by Dr. Buzzard; in others only the supinator longus. When the whole group is affected the patient is unable to lift his arm—it hangs powerless by his side: he cannot bend the forearm at the elbow owing to paralysis of the biceps, and yet he can extend it, the triceps having escaped. It is said that in this state muscular atrophy and the disturbances of electrical contractility are less pronounced than in the more classic form. In one of my female patients not only was the Duchenne-Erb group of muscles affected, but there was also paralysis of the supinator longus and of the extensors of the wrists and fingers: the muscles of the pelvis, legs, and feet also became weak. It was a mild form of an acute multiple paralysis, accompanied by severe pain and rapid atrophy; it resembled the widely distributed paralysis met with in polyneuritis, both as regards pain in the muscles, the distribution of the paralysis, and the rapidity of its development: the knee-jerks, however, were exaggerated. In fatal cases the paralysis invades the muscles of respiration—for example, the intercostals, the diaphragm, and the muscles of the larynx. The muscles concerned in deglutition, too, become affected; so that the patient lies in bed in the dorsal decubitus, perfectly helpless and unable to eat. Before the legs become paralysed the muscles are usually tender and the knee-jerks exaggerated. In one of my chronic cases the symptoms closely resembled those of bulbar paralysis: the tongue gradually became smaller, and speech and swallowing difficult; but there was never the dribbling of saliva met with in the classic medullary lesion.

In the early stages the skin is frequently sensitive to the prick of a pin; but later it may become analgesic or anæsthetic, always bleeding, however, when pricked—a circumstance that removes it from the category of hysteria. According to Guinon the anæsthesia may be confined to those parts that have been brought into direct contact with lead; or it may be widely distributed, amounting to hemianæsthesia. Frequently there is tremor of the affected muscles, also of the naso-labial muscles and of the tongue. In one case Dr. Buzzard found the third nerve affected, causing ptosis, with abolition of movements of the superior, inferior, and internal recti muscles; the pupil was dilated and did not react to light. The external rectus alone may be paralysed. Oculo-motor paralysis, when present, is usually bilateral; the abducens, like the extensor muscles generally, is most apt to be affected. Diplopia was observed in some of my own cases without any apparent muscular defect; nystagmus also. The musculature of the bladder may become affected, causing incontinence.

One of the gravest effects of lead upon the nervous system is

neuro-retinitis. This may set in rapidly without any concurrent kidney disease. It is often associated with headache and epileptiform seizures. Vision may be very slightly obscured, or it may be lost temporarily or permanently. Attacks of transient blindness occur in the absence of neuro-retinitis, and seem to be central in their causation, and probably toxic. Temporary loss of vision occasionally occurs during lead colic; it may be the result of the accompanying high arterial blood-pressure, or of toxæmia; there may be no albumin in the urine. It may come on without headache, and be independent of neuro-retinitis. Mr. Simeon Snell found primary optic atrophy due to lead in a file-cutter. Occasionally hemianopsia occurs; it is usually transitory. In the acute cerebral form of plumbism the borders of the disc are swollen, ill-defined, and irregular; the disc itself is hyperæmic and mottled; the vessels are obscured, or, if observable, they are narrowed, and have delicate white lines running along their border; the veins are distended, and occasionally hæmorrhages are seen just at the border of the disc or in the retina. This form of neuro-retinitis is generally associated with eclamptic seizures, and is usually followed by optic atrophy. It is a sign of acute plumbism rather than of the chronic forms of the disease. It may occur in young women who have only worked for a few weeks or months in a lead factory. Whether vision be regained, or permanently lost, albumin may never be present in the urine. The malady differs, therefore, from the neuro-retinitis met with in chronic kidney disease. De Schweinitz and others are of the same opinion. Since the abolition of female labour in lead works a few years ago encephalopathy and permanent blindness are not so frequently observed as formerly.

Instead of regarding optic neuritis as in any way specially related to and caused by saturnine poisoning, it has been attributed to deranged menstruation; to uræmia; or to lead acting mechanically, and inducing rapid effusion into the ventricles and subarachnoid spaces, the sheath of the optic nerve becoming thereby distended. Amenorrhœa can play but a minor part in its causation, for the optic neuritis occurs also in cases attended with menorrhagia. It may be a descending neuritis, or be due to distension of the sheath of the nerve. It is invariably met with in acute lead encephalopathy when there are signs of increased intracranial pressure, the convolutions of the brain being found flattened post-mortem. Lead itself may not be without some direct malign influence upon the disc and retina. Leuber and Deutschmann have suggested that optic neuritis may be caused by irritating or infective particles carried by the subarachnoid fluid from the cavities of the brain to the sheath of the optic nerves. Many such adverse circumstances may concur to produce it, but the two most important are the direct or indirect action of lead salts upon the disc and retina, and the effect of increased intracranial pressure; for in fatal cases the brain is frequently found dry and firm, extremely pale, and the arteries contracted. The movements of the iris vary with the condition of the optic nerve and retina. When there is neuro-retinitis the pupil is dilated.

Parelle draws attention to a very interesting sequel of lead poisoning. In fifteen cases of plumbism Tanquerel noticed embarrassment of speech, but he did not correlate it with general paralysis: it was left for Delasiuve to demonstrate this. The affection apparently occurs with considerable frequency in France, and although it is met with principally amongst white-lead workers other persons do not escape. Contrary to what takes place in alcoholic pseudo-general paralysis, the influence of heredity is not observed in saturnine cases; nor is the affection met with in women. Forty to fifty years of age appears to be the most susceptible period. *Saturnine pseudo-general paralysis*, though aggravated by alcoholic habits, occurs in those who are temperate, and must therefore be regarded as the result of lead toxæmia. It differs from ordinary general paralysis in its sudden onset. Violent delirium is frequently its first symptom; or there may be an epileptiform seizure, nightmare, or hallucinations. These latter, whilst pretty constant in saturnine general paralysis, are very rare in the ordinary form. In other words, in addition to the usual encephalopathic symptoms due to lead, there are nightmare, hallucinations of sight, imaginary terrors, and confused ideas of being pursued or of being poisoned, just as in delirium tremens. Occasionally the approach of the disease is less characteristic, and is slowly progressive. The patients steal like ordinary general paralytics, and they have grand ideas. The later features are muscular weakness, embarrassment of speech, weakness of the intellectual faculties and of the memory. The patients sleep badly, and become excited towards evening. Following upon this comes a stage of physical weakness, when the patients cannot stand—they are obliged to rest; some are completely paraplegic, others hemiplegic and covered with sores. Trembling of lips and tongue, and sometimes, too, of the arms and legs, are very pronounced. Speech is generally most embarrassed at the beginning, and, if anything, it is apt to be more pronounced in saturnine than in ordinary general paralysis. The loss of memory is complete; and the general hebetude of the intellectual faculties is so noticeable that the patient, even in the early period, resembles a general paralytic in the last stage of his illness. One point of difference between saturnine general paralysis and the ordinary form is the tendency to amelioration in the former. Even after the third stage has been reached, and there have been epileptiform seizures, ideation may return, the paralysis diminish, the power of walking improve, speech become more distinct, and the patient become more intelligible. Concurrently with this improvement, however, he becomes extremely irritable on provocation.

Early withdrawal of the patient from the influence of lead may be followed by convalescence in from six to twelve months. The disease tends to cure itself; but in some cases, and without any explanation, there is a downward course, the fatal termination being precipitated by an apoplectiform or epileptiform attack. If a patient poisoned by lead subsequently falls into general paralysis it does not follow that it is saturnine; but when in a general paralytic we have a history of plumbism,

this is a point in favour of the case being one of pseudo-general paralysis. The mode of onset of the two diseases is, indeed, slightly different. A brusque inception suggests pseudo-general paralysis. Epileptiform seizures belong rather to the early stage of this disease. There is not the permanent inequality of the pupils, and the trembling is more widely distributed in pseudo-general paralysis than in the ordinary form. Besides being more generalised the tremor is also more intermittent, more pronounced, more spasmodic; and it appears first of all in the hands. The embarrassment of speech, too, is greater, particularly in the early stage. Disturbances of sensation, which are rare in true general paralysis, are frequently noticed; and usually consist in anæsthesia, especially in loss of the sensation of pain. In ordinary general paralysis the disease is slowly developed, is progressive, and tends to death; in that of plumbism, on the contrary, the progress is quick, and even after serious and ominous symptoms have appeared, these may improve and health be slowly regained. Only a few cases have ended fatally, and in these the post-mortem appearances were those of ordinary general paralysis; on chemical analysis, however, lead was found in the brain.

In another group of cases symptoms of muscular inco-ordination may suggest a *pseudo-tabes* due to lead poisoning. Putnam has met with three cases, Teissier and Raymond each with one. I have also seen a similar case. In such patients there is inability to co-ordinate movements accurately, probably from loss of the muscular sense; in other cases there is no true inco-ordination, but a disordered movement due to loss of power in certain groups of muscles, the gait being high-stepping, consequent upon paralysis or weakness of the extensors of the foot. In Raymond's case the symptoms appeared in a male after being exposed for only two months to lead dust; and in him the inco-ordination in the legs set in whilst that of the arms was disappearing. All of Putnam's cases were in women, aged respectively 15, 27, and 45 years; the muscular inco-ordination was aggravated by closure of the eyes. It was followed by atrophy of the muscles, impairment of vision, diplopia, girdle sensation, loss of the muscular sense, exaggerated knee-jerks, incontinence of urine, and the presence of lead therein. The point specially noteworthy in these cases of pseudo-tabes, as in saturnine pseudo-general paralysis, is the rapid improvement under treatment; so much so as to suggest a functional and not an organic disease. Most of the symptoms have been explained by a supposed peripheral lesion; but in a case reported by Morris of Charlestown, in which there were the symptoms of saturnine pseudo-tabes with exaggerated knee-jerks, there was degeneration of the posterior and lateral columns of the spinal cord. It is cases such as these and pseudo-general paralysis that oblige us at this point to remark that in many cases of saturnine peripheral neuritis the lesion is not entirely peripheral but central, or a combination of both. The changes in the nerve-centres may be so slight, or so purely dynamic, that toxic conditions of blood, by deranging the nutrition of ganglion-cells in the spinal cord, would indirectly affect the peripheral nerves far

removed from these cells. Owing to its distance from these trophic central cells the peripheral portion of the nervous system is necessarily the more vulnerable. Nutritional changes affecting the ganglion-cells in the cord influence the peripheral terminations of the nerves; and changes affecting the periphery are known to influence the central cells. It is true that anatomical changes are conversely indicated in the peripheral nerves, but they are detected rather by the greater readiness with which they respond to microscopical staining reagents. Dynamic conditions may affect central cells in such a manner that we cannot demonstrate them—a statement not only applicable to the spinal cord, but to the brain in lead encephalopathy. In Minakow's, Oeller's, and Drummond's cases pathological changes were found in the anterior cornua of the spinal cord. Before answering the question whether in lead paralysis the lesion is peripheral or central, let us accumulate facts bearing upon this subject from the experimental as well as the clinical side.

In feeding animals with lead salts effects are produced with varying rapidity. On absorption of the lead there occur loss of appetite, a peculiar nervousness, constipation or diarrhœa with dark stools, albuminuria, and rapid emaciation; death generally ensues when one-third of the body-weight has been lost. Many female rabbits thus treated died, and on chemical examination we found lead in the fœtuses. The tendency for animals to become pregnant is diminished, and in my own cases the male rabbits seemed to lose all sexual desire. Most of the animals were paralysed first in the hind legs, so that in walking they dragged the limbs, or they progressed with a peculiar skipping movement: subsequently the fore limbs became paralysed and the animals died in convulsions. At the post-mortem examination the lungs and kidneys were found congested, but the peculiar feature of all cases of acute lead poisoning—in human beings as well as the lower animals—is the extreme rapidity of decomposition, and the very strong odour that is generated thereby. A few hours after death the corpse is already putrid. The readiness with which paralysis is produced in the hind limbs of animals gives us the opportunity of studying the effects of lead upon the various organs and peripheral nerves. Déjerine maintains that there is a combined lesion of the anterior roots and their cornual cells, with peripheral neuritis; whilst Gombault and Charcot attributed the disordered motion and sensation to a special form of peripheral neuritis; the neuritis being segmentary and periaxial, and therefore distinct from the Wallerian form of degeneration consequent upon section of the nerve. In periaxial neuritis the axis-cylinder escapes; the alteration is confined to several of the annular segments of Ranvier, whilst above and below these the nerve-fibre is normal. The lesion differs, therefore, from that met with in Wallerian degeneration, in which when the fibre is altered in its course the change extends to its remotest part. Since the integrity of the axis-cylinder is maintained the morbid state may be remediable; sometimes, however, even in periaxial neuritis, the axis-cylinder undergoes fragmentation, and then there occurs a peculiar modification of Wallerian

degeneration, which still may be followed by a regeneration of the nerve throughout its entirety. Gombault's views have been combated by Pitres, who does not believe in the integrity of the axis-cylinder in periaxial neuritis. These segmentary neuritides are found in a large number of infective and toxic diseases. The frequency with which Brissaud found them in tuberculous and cancerous patients, in old people, and in peritonitis, has thrown some doubt upon the interpretation of them in lead poisoning. It is a question whether we can regard them as true neuritis, or simply as a myelino-neuritis such as is met with in disseminated sclerosis. It is equally true that saturnine periaxial neuritis occurs, and that the nerves undergo regeneration; this explains the rapid and spontaneous cure of the paralysis which takes place within two or three weeks on cutting off the supply of the poison, and the fact, too, that the paralysis may be very slight.

Most neurologists insist that the lesion in lead poisoning is peripheral; and in chronic cases of wrist-drop the peripheral nerves are certainly the seat of well-marked interstitial neuritis; but are the anterior horns of grey matter in the spinal cord quite healthy? Déjerine found changes in the anterior roots corresponding to those in the altered peripheral nerves, and so did Vulpian. We must remember that in acute lead poisoning in man and animals, when the onset of paralysis has been rapid, the most careful microscopical examination may fail to detect pathological changes in the nerves. There is another possible interpretation of the relation of spinal cord and peripheral nerve changes. Drs. Laslett and Warrington have published in detail the pathological changes found in the nerves and muscles of a house painter who had "wrist-drop" and atrophied muscles. On microscopical examination the posterior interosseous and ulnar nerves were atrophied, and also the anterior roots of the sixth, seventh, and eighth spinal nerves, while the corresponding posterior roots were normal. Of the extensor muscles of the hand 90 per cent of the fibres were atrophied, but still retained their cross striation. There was very little evidence of fatty degeneration, but the connective tissue was increased. The muscle-spindles were unaltered. The anterior cornual cells in the sixth and seventh segments of the spinal cord were found to be changed. The nucleus was situated eccentrically, and the Nissl bodies were dispersed over the body of the cell, with marked evidences of chromatolysis. On an average 1 in every 4 cells had become altered. While admitting that lead primarily acts upon the central nervous system, Drs. Laslett and Warrington are of the opinion that in their patient, owing to the excess of change in the peripheral nerves, the spinal cord lesion was secondary to the peripheral neuritis, an opinion which the eccentric position of the nucleus, they maintain, confirms. On this view the anterior cornual changes would not be the result of the action of lead upon the spinal cord, but would be consequent upon the altered state of their functional activity, the result of atrophy of the axons of the cells, or, in other words, secondary to a lesion of the axis-cylinder of the nerves—the "réaction à distance" of Marinesco. The

incidence of paralysis principally on the muscles most used and therefore most liable to fatigue is in favour of a central cell origin.

As to the electrical condition of paralysed muscles, it is sufficient here to state that in lead palsy there is marked loss of faradic excitability; whilst there may be normal or exaggerated response to galvanism if the paralysis be not of long standing. Occasionally in plumbic paralysis a small indolent swelling on the back of the wrist is noticed; it was first described by Gubler, and it conveys the impression of thickening of the extensor tendons.

Considering its prevalence plumbism is not a frequent cause of *insanity*; nor does mental derangement occur without some premonition. Now and again a case is met with presenting symptoms akin to hysteria or alcoholic intoxication, which are followed by convulsions, coma, and death; but in others symptoms of melancholia advance slowly, or there is acute delirium accompanied by hallucinations, with or without affection of speech, which is apt to be remittent, and to recur at night. Occasionally the delirium like that of acute mania develops suddenly, the only complaint having been headache. It is of a noisy character, and so violent is the patient that it may be necessary to restrain him. In the intervals consciousness may be regained. The patient may be blind, the urine quite free from albumin, and the temperature rather below than above the normal. As the paroxysms keep recurring with increasing severity, the medicinal means adopted to restore quietude and induce sleep—for example, bromides, morphine, chloral, or hyoscine—unfortunately tend only to precipitate the sufferer into deep coma, from which he never rallies; death being preceded by a rapid rise of the temperature. Cases of monomania have been recorded. When mental symptoms arise in plumbism, setting aside acute encephalopathy, they have usually been part of a series resembling general paralysis, such as we have described.

In deaths from plumbism lead is generally found in the internal organs. In my own patients Prof. Bedson found the largest quantity of lead in the liver, and next to it in the nervous system. Gusserow found most in the muscles. It is found in the bones, in the kidneys, in the testicles, in the fœtuses of lead-poisoned animals, and in ovarian tumours. Prof. Bedson examined the milk of a nursing white-lead worker under my care, but failed to find lead in it. Dr. Honeyburne has shewn that in plumbism an increased amount of iron is deposited in the liver, an interesting observation in connexion with the anæmia of saturnine poisoning.

What is the relation of saturnine poisoning to *abortion*? Does lead actually pass through the placenta? That it does so seems proved by its presence in the fœtus. Porak has experimentally demonstrated the passage of arsenic, copper, lead, mercury, and phosphorus through the placenta. In autopsies on cases of poisoning the possibility of such poisons having traversed the placenta should be borne in mind. Porak found that lead is very poisonous to guinea-pigs, but that abortion in them is less frequent than in other animals; although death of the

fœtus is very apt to occur. It happened thrice out of six experiments. In other animals still-birth was a constant feature, and after death there were found dropsy of the ventricles of the brain with thickening and slaty discoloration of the ependyma of the third, fourth, and lateral ventricles. This cerebral lesion and the presence of lead in the central nervous system explain the paralytic phenomena observed in fœtuses at the time of their birth, and the convulsions and early death of the children of lead-workers. Rennert has clinically confirmed Porak's observations. He found the children of potters suffering from plumbism to be hydrocephalic, and that they died within a few days after birth from convulsions. This is my own experience. Lead passes readily through the placenta, and diffuses itself through the fœtus, being found in the liver, in the nervous system, and in the skin. It is eliminated slowly by the fœtus. We found 0·1 milligramme in the liquor amnii, and in five fœtuses there was 0·09 milligramme of lead in each. The blood also contained a trace. The placenta has apparently little power in fixing lead, as is seen from the following. Ballard, quoted by Treille, gives the details of 100 pregnancies in which one or both parents were the subjects of saturnine poisoning. Abortion occurred in 40 instances. There were 26 premature confinements and 32 accouchements at normal term. Of these 32 births 60 per cent were still-born, 26 of the children died within the first year, so that at the end of twelve months less than 20 per cent of the children were alive. Constantin Paul gives as the result of his enquiries of 141 pregnancies, 82 abortions, 5 still-births, and 4 premature confinements, while of the 50 children born alive 20 died during the first year and 15 before the third. The accidents observed in saturnine intoxication in the newly-born depend apparently upon accumulation of the poison in the central nervous system: first, because there is dropsy, with thickening of the ependyma, of the ventricles of the brain; and, secondly, because when born alive the fœtuses soon die, paralytic, probably from fixation of the poison in the brain. It has been stated that lead is only eliminated by the kidneys when the urine is albuminous. This is incorrect: we frequently found traces of lead in the non-albuminous urines of female patients. In the bile fairly large quantities of lead may be found. Saliva also may contain it and we found it in sweat, but not in the mammary secretion. Dr. Dixon Mann has not only demonstrated that by far the largest quantity of lead leaves the system by the stools, but that in certain cases its presence can be demonstrated in the fæces when the urine does not contain a trace of the metal.

It is said that iodide of potassium favours the elimination of lead from the system, but the increase is hardly perceptible. In plumbism there is defective elimination both of urea and of uric acid. Retention of uric acid in the system is regarded as the cause of *gout* in plumbism, owing to lead diminishing the alkalinity of the blood, lessening the solubility of uric acid, and thereby hindering its excretion by the urine. Sir Wm. Roberts doubted the direct determination of gout by lead, and believed that both the gouty diathesis and lead poisoning have the same

tendency to precipitate crystalline urates in the tissues or fluids of the body. This saturnine uratosis, he maintained, is simply reinforced by a previously existing gouty tendency. In the North of England we seldom meet with gout and plumbism, and in the few cases in which I have observed it there has been a strong hereditary disposition to gout. In several cases the elimination of lead by the kidneys seemed to be inversely proportional to that of uric acid. That lead does favour the retention of uric acid in the system is probable; and from the readiness with which gouty seizures in the London hospitals have followed the administration of small doses of plumbic acetate, gout and plumbism seem at first sight to be causally related to each other. It is difficult to explain why the association of plumbism and gout should be so frequently observed in London and so seldom in Newcastle and Edinburgh. It is probable that the explanation is to be found in the difference in the food, external circumstances, and hygienic precautions, and in the habits of the people as regards the use of stimulants, beer disposing to uratosis more than whisky. The fact remains that in those districts where gout is infrequent the disease is not promoted by chronic lead poisoning; but where gout prevails even small doses of lead seem sufficient to produce gouty symptoms.

During lead colic the urine and urea are diminished; but the crisis once over, they gradually rise to near the normal. Vomiting, diarrhœa induced by aperients, and the absence of food, doubtless favour this deficiency. The total nitrogen eliminated was found by Surmont and Brunelle to be diminished during colic. In my own cases the urea was only a half or a third of the normal. Potain states that the liver is diminished in size during colic; but this is doubtful, as at this particular time, owing to the retraction of the abdomen, the liver ascends under the costal arch, becomes less oblique, and diminished in its vertical diameter. Hepatic function is deranged, for pathological urobilin may be found in the urine. The glycogenic function is particularly disturbed during colic, as the administration of syrup is said to be followed by glycosuria; but in my own experiments upon rabbits the liver always contained glycogen.

As regards the elimination of uric acid in plumbism there is considerable difference of opinion. Sir A. Garrod maintains that it is diminished during the attack. Surmont and Brunelle found it diminished in four out of eleven cases, and increased after colic; the diminution or increase of the uric acid was in no way proportional to the severity of the colic, and old saturnine patients were apt to pass it in excess. In my own clinical experience the amount of uric acid has varied; it has sometimes risen as high as 12, 16, and 21 grains per diem; the normal being 7 to 15 grains, whilst the lowest was 2 grains. In the latter case the urea also was frequently much below the normal; and it is interesting that on the days the patient passed the largest quantities of urea she was free from headache. The urine generally contained a trace of lead. The elimination of lead and of uric acid may be inversely related to each other; as if the presence of the metal in the blood favoured the retention of uric acid in

the system. Surmont and Brunelle found the amount of creatin and hippuric acid increased, an interesting point, seeing that the total nitrogen and urea are diminished; it indicates how profoundly metabolism is affected in saturnine poisoning. Goetze of Würzburg maintains that in the arthritic attacks and colic uric acid keeps below the normal, and remains low for some time after the attack. During chronic plumbism it fluctuates within the limits of the normal. He also found that in the acute attacks chlorides were diminished and increased subsequently. Of the elimination of phosphoric acid by the kidneys not much is known. Taking 30 to 50 grains of phosphoric anhydride as the daily average in health, I found that it varied from 25 to 77 grains. Goetze found it always low in chronic plumbism. Some writers have noticed hæmatoporphyrin in the urine after lead colic.

The **morbid anatomy** of acute plumbism is practically nil. In lead encephalopathy the brain may be shrunken and dry; it may appear as if it had been compressed, all the blood-vessels being constricted. The brain substance may be pale and extremely firm, or pale and œdematous as in uræmia. The small intestine may be extremely contracted in places. The kidneys are generally stated to be atrophic and the seat of interstitial nephritis, but this is principally found in the chronic cases. In acute lead poisoning, both in man and animals, the epithelium of the convoluted tubules is the seat of cloudy swelling, becoming fatty, granular, and rapidly breaking down; the débris may be seen in the interior of the tubules. The change in the kidneys is therefore parenchymatous at first, and is frequently accompanied by some degree of glomerular nephritis; for the afferent vessel to the glomerulus may be seen surrounded by numerous round cells. Bowman's capsule is thickened, and there is a multiplication of the cells that line its interior or of those that lie between the coils of the capillaries. From the external surface of the glomerulus round cells may be observed penetrating between the convoluted tubules, causing an increase of the connective tissue at this particular part of the kidney, and giving rise therefore to an interstitial nephritis secondary to the parenchymatous. While insisting that tubular nephritis is the primary lesion in lead kidney I am not ignorant of the views held by other pathologists as to the condition of the interstitial tissue; but changes therein seem rather to follow those occurring in the tubular epithelium. Ollivier mentions parenchymatous nephritis; and in the kidneys of animals experimentally treated by Charcot and Gombault there were degenerated epithelial cells in the tubuli uriniferi, with proliferation of small round cells around those tubules only in which the epithelium was affected. Coën and d'Ajutolo found in rabbits, killed at varying periods after the administration of acetate of lead, that the epithelium of the urinary tubules first became swollen, then degenerated and shed; and that in the more chronic cases there was a glomerulitis followed by thickening of the vessels and interstitial nephritis. Hirsch's more recent experiments upon guinea-pigs, detailed in his Thesis for the Doctorate in Medicine of Leipzig University, rather led

him to regard the epithelial and interstitial changes as occurring simultaneously; but as he states that epithelial degeneration is constant in all lead kidneys, and is the specific lesion caused by lead, he, too, is clearly of opinion that it is one of the earliest and principal effects of lead.

Lead acts very injuriously upon the eliminating organs. The liver, like the kidneys, is the seat of marked changes. It is in this organ that the largest amount of lead is found on chemical analysis; it looks fatty, and microscopically the hepatic cells are atrophied and granular, or shew advanced fatty change. In some cases there is intercellular cirrhosis; in others a marked increase of connective tissue between the lobules. Whatever view we take of the pathology of plumbism, it must be admitted that lead rapidly deranges metabolism. It destroys the functional activity of the liver and kidneys, slowly inducing changes within their secreting cells; and although we cannot forget that certain symptoms of encephalopathy depend upon the presence of lead in the brain, they are more probably caused by animal poisons retained within the system during inadequate hepatic and renal elimination, a proof of which auto-intoxication is that in some of my cases of fatal saturnine encephalopathy, characterised during life by convulsions and coma, not the slightest trace of lead was found in the brain after death. This opinion, fully expressed in my Goulstonian Lectures (1891), has met with considerable acceptance. In America the treatises of Hughes and Carter, and of Miller and Ring, lend the weight of their authority to it.

It is known that the elimination of metallic poisons from the body is protracted over a lengthened period, but can lead be deposited in an inert form in the tissues for years, and becoming redissolved, suddenly overwhelm the individual and produce fresh symptoms of lead poisoning? Seventeen years ago a female lead-worker, then aged 19, was under my care in the Newcastle Infirmary on account of encephalopathy and convulsions followed by blindness. A few months afterwards sight was regained and the patient left the hospital. She never returned to the lead works, nor from that date until her readmission into the Infirmary seventeen years afterwards had she been brought into contact with lead in any form. She married, and is the mother of six children, of whom five survive. She has had three miscarriages. The most careful inquiry fails to elicit a history of syphilis or alcoholism. Patient was readmitted into the Infirmary suffering from headache, double internal squint, diplopia, double optic neuritis, and almost complete loss of vision. Only once or twice had she vomited. Her internal organs, generally speaking, were healthy, but her menses had been suppressed for nearly a year. There was no albuminuria, but Professor Bedson found lead in the urine. Under the administration of magnesium sulphate and potassium iodide sight was for a second time restored and the patient made a good recovery. Is it possible that lead could have lain inert in the body all these years, and becoming redissolved, be the cause of fresh poisoning? There is much to support this

view, for the relapse, if it was a relapse, was as unexpected and as fulminating as a primary attack of lead encephalopathy.

Diagnosis.—In the stage of acute colic the extreme pain in the abdomen might be mistaken for severe intestinal cramp, for peritonitis, or appendicitis, but there is usually no rise of temperature, and the abdomen is generally retracted. No distended coils of intestine are noticeable. The abdominal pain, though sometimes relieved, is as a rule increased by pressure, when it is observed to be more or less unilateral, and associated with pain along the course of the vagus in neck on the same side; the pulse is small. The history of the case, the presence of a blue line on the gums, distinct cachexia, and a peculiar restlessness suggest plumbism, the diagnosis of which would be confirmed by the detection of lead in the urine on chemical examination. This may be done as follows. Evaporate 50 cubic centimetres or 2 ounces of urine to dryness; ignite the residue, extract the lead from this by dilute hydrochloric acid. Precipitate the lead as sulphide by means of sulphuretted hydrogen or ammonium sulphide. The objections to this procedure are its tediousness and the necessity for the preliminary destruction of organic matter. To the method for detecting lead in urine mentioned by von Jaksch in his *Klinische Diagnostik*, which Drs. Abram and Marsden of Liverpool found both accurate and simple, these objections do not apply. A strip of magnesium is placed in the fluid to be examined. Ammonium oxalate in the proportion of 1 gramme to 150 c.c. is added. If lead be present it is deposited on the magnesium. Some deposit is seen within half an hour, but it may require a longer exposure. The slip is then washed with distilled water and dried. In order to confirm the test (*a*) warm the slip with a crystal of iodine upon it; yellow iodide proves the existence of lead—the probability of its being cadmium need scarcely be entertained; (*b*) dissolve the deposit in nitric acid and apply the usual tests for lead. In making use of this method care must be taken to have the surface of the magnesium bright and free from the presence of any oxide. This is an extremely delicate test, capable of detecting 1 part of lead in 50,000, whether the metal be dissolved in water or contained in an organic liquid like urine. The detection of lead in the internal organs and bones in a cadaver is of considerable medico-legal importance as pointing to lead poisoning, for the organs of persons who have died from plumbism generally contain traces of the metal. Normally there is no lead in the human body, but the same cannot be said of arsenic and some of the other metals.

Bilateral paralysis suggests a toxic cause. Usually but not always both wrists are affected in lead poisoning. Affection of the muscles of the upper extremity, particularly the extensors of the wrists and fingers, rather than those of the lower limb, is suggestive of saturnine as against arsenical and alcoholic paralysis. Although not wholly absent, there is, generally speaking, less tenderness on grasping the muscles in lead than in either alcoholic or arsenical paralysis; whilst, if anything, there are more rapid atrophy and greater sensory disturbance in arsenical than

in saturnine poisoning. At one stage of the illness lead paralysis may resemble anterior poliomyelitis and progressive muscular atrophy; but in plumbism the paralysis is usually limited to the extensor muscles, especially those of the wrists and fingers, whereas in the spinal cord lesion both flexors and extensors are involved. Tremors may be present, but they are distinguished from the movements observed in mercurialism by being less wide in their range, usually ceasing during rest, and by being less apt to remit.

In lead paralytics there is usually a history of colic. The loss of power primarily affects the extensor communis digitorum, and later the other muscles of the forearm supplied by the musculo-spiral nerve with the exception of the supinator longus; a peculiarity which distinguishes it from a local lesion of that nerve. When the paralysis is well marked, the affected muscles fail to respond to induced electrical currents, whilst to a slowly interrupted galvanic current they usually respond freely. Dr. Buzzard has found this test to be of signal service in the absence of other physical signs or a suggestive history. Like myself he, too, has found the supinator longus occasionally affected in lead poisoning; so that the dictum of Duchenne on this particular point must admit of exceptions. It was Remak's observation that the cells in the anterior horns of the grey matter of the spinal cord represented muscles that are functionally associated; hence when the supinator longus was affected the brachialis anticus and biceps were at the same time involved, thus forming the "forearm type" of lead palsy. Drs. Ferrier and G. Yeo, by irritating the brachial plexus of the monkey, have experimentally demonstrated that each motor root represents rather a distinct functional combination than contiguity in peripheral nerve distribution; and that the movement of supination is subserved by roots coming from a part of the cervical enlargement higher up than that which brings about extension of the wrists. Thus physiologists seek to explain the frequency with which the supinator longus escapes in lead poisoning, whilst other muscles supplied by the musculo-spiral nerve are affected.

Prognosis.—The prognosis is favourable in the stage of colic and vomiting. Death does not occur in uncomplicated lead colic. When, however, the attacks of colic are renewed from time to time, and recur over a long period in patients whose health is deteriorated, and in whose urine there is albumin, the illness must naturally be regarded as grave. Under electrical and medicinal treatment, uncomplicated saturnine paralysis generally disappears; but in some cases the recovery is extremely slow and at the best is incomplete, for weakness of the wrists endures a considerable time. The prognosis of acute lead encephalopathy with convulsions is extremely grave. Not only is there danger of the patient dying in the seizure without regaining consciousness, but should the symptoms subside, the mental condition for some time afterwards may remain unhinged, speech and memory may be defective, or blindness may be permanent.

The **treatment** of lead poisoning is preventive and curative. Lead

pipes for the conduction of drinking-water should not be used, and should be replaced by pipes made of iron or glass. Lead cisterns for the storage of water for culinary purposes should not be allowed. All drinking-water should be transmitted direct from the main into the houses, and before being used in the morning the water should be run off for a few minutes at first, so as to empty the lead pipe. The addition of carbonate of lime, magnesian limestone, or silica to the water, provided no excess of carbonic acid be present, frequently allows of the formation of a protective covering on the interior of the pipe. The presence of micro-organisms in water increases its solvent power upon lead, owing to the influence of chemical products formed during their multiplication; hence sewage-polluted water—which also contains chlorides, nitrates, and nitrites—is especially dangerous. To stock the reservoirs with fish is an inexpensive and efficient method of reducing the plumbo-solvent action of moorland water.

As regards industrial lead poisoning the Home Office has issued regulations, the strict enforcement of which in factories has been beneficial. Men and women therein employed should be medically inspected once a week, and an increasing anæmia should be regarded as a disqualification. Frequent ablution, the wearing of overalls and respirators, and washing before eating diminish the risk to some extent; but the women are unable to take the prescribed baths at their menstrual periods. Washing the hands with water containing hypochlorite of soda or paraffin is a good preventive. Acidulated drinks, composed of water in which sulphuric acid and magnesium sulphate are dissolved, and to which lemon has been added, are provided in all white-lead factories, and the work-people are encouraged to drink freely of them; but the preventive power of these drinks is feeble; an excess of free sulphuric acid in the water would redissolve any sulphate of lead formed in the alimentary tract, and the tendency would be favoured by the presence of fresh lemon juice. Besides, sulphate of lead is soluble in the hydrochloric acid of the gastric juice. The alcoholic habit strongly predisposes to plumbism. Milk should form a large part of the dietary of the work-people; and no person should be allowed to work in a white-lead factory before breakfast, for clinical experience and experiment have demonstrated that the presence of food in the stomach diminishes the solvent influence of the gastric juice upon lead. The addition of a small quantity of sulphur to the milk increases its protective powers.

For the colic, if not severe, a mild purgative, such as magnesium sulphate or castor oil, may be sufficient; but, should it be accompanied by vomiting, effervescing mixtures may be tried, and enemas of warm water and olive oil resorted to. Should the abdominal pain be severe, small doses of tincture of opium or of belladonna may be added to the aperient; or a hypodermic injection of morphine and atropine may be administered, or belladonna fomentations applied. A mixture of magnesium sulphate and potassium iodide generally acts well. Occasionally it is difficult to relieve the colic, but it will generally yield to the influence

of a warm bath. When the colicky pain and vomiting have been relieved, or when colic alone is present, monosulphite of soda, in one-third or half-grain doses every two or three hours, has a wonderful influence in soothing the general symptoms. In a mild case abdominal pains and paralysis quickly disappear under its influence.

As an eliminant potassium iodide still finds favour, and rightly so; but in the early part of the treatment of acute plumbism it should be used with caution, for under its use lead, which has been deposited in the tissues and is therefore inert, might be redissolved, and fresh symptoms of saturnine poisoning reappear. Occasionally the drug causes albuminuria. In a female patient transferred to my care by my colleague Dr. G. R. Murray, the administration of five-grain doses of potassium iodide was followed by a rise of temperature (101·8° F.) and the presence of albumin in the urine. On discontinuing the medicine the temperature fell and the albuminuria disappeared, but on renewing the potassium iodide the albuminuria returned. The bromide is also efficacious. Dr. Burney Yeo quotes Semmola as having found electricity useful. The patient is placed in an acidulated bath, and one pole of the continuous current is applied to the tongue while the other remains in the water: or, without using the bath, one pole may be applied to the tongue and the other to the epigastrium. It is stated that the blue line disappeared from the gums in a few weeks, and examination of the urine shewed increased elimination of lead. For saturnine paralysis, which is sometimes very obstinate, electricity, massage, and nux vomica, with potassium iodide, or the subcutaneous injection of strychnine, are useful; and for the anæmia, which remains after the painful symptoms have disappeared, tablets of bone-marrow have given encouraging results.

For lead encephalopathy, when convulsions rapidly succeed each other, the inhalation of nitrite of amyl is very serviceable. Under its influence the pulse regains its softness and recovers its frequency. As the urine is often suppressed, the subcutaneous injection of pilocarpin may be called for.

Seegelken of Jena has successfully practised tapping of the lumbar region of the spinal canal in the coma of lead poisoning. A patient after suffering from lead colic had been seized with recurrent convulsions and unconsciousness. The urine was non-albuminous. In the intervals between the convulsions the right arm and leg were observed to be paralysed. As coma endured for two days Seegelken had recourse to lumbar tapping, removing sixty grammes (a little less than two ounces) of cerebrospinal fluid with a pressure of 310 mm. of water, which gradually fell to 80 towards the end of the operation. Shortly after the puncture the patient gradually regained consciousness; that evening he sat up in bed, and within thirty-six hours all cerebral symptoms had disappeared. On the hypothesis that the convulsions and coma of lead encephalopathy are due to acute œdema of the brain, it is interesting to note that the fluid as it first flowed was clear, serous, cerebrospinal: whilst towards the end it was cloudy, a circumstance which suggested to the operator its encephalic

origin. E. Mosny performs lumbar puncture in lead colic, especially when there are cerebral symptoms, and on centrifuging the fluid, which is clear like water, he finds on microscopical examination evidence of a distinct lymphocytosis, similar to that met with in tuberculous meningitis. I have been present when Mosny has performed lumbar puncture, and have thus had the opportunity of confirming the presence of the excess of leucocytes, due probably to a reaction on the part of the cerebrospinal membranes to the lead. In the Victoria Infirmary, Newcastle, I have practised lumbar puncture in lead poisoning, and have drawn off as much as an ounce of clear fluid at a time; but, although all the details of the technique as regards centrifuging and staining were carefully followed, there was no lymphocytosis such as I had observed with Mosny in Paris, nor on chemical examination of the cerebrospinal fluid was there found any trace of lead in two cases of plumbism.

Arsenic

Of the cases of criminal poisoning in this country those by arsenic used to form the largest number, and accidental poisoning by arsenic the smallest. Lately conditions have changed. In the three years ended 1903 there occurred 100 deaths from arsenic, 47 males and 53 females. In these are included 12 deaths by suicide, 8 males and 4 females; the remaining deaths were the result of accident and of drinking contaminated beer. There was no case of criminal poisoning. The comparative tastelessness of the drug is one reason why it was so frequently resorted to for criminal purposes. The metal itself is innocuous; but when acted upon by the juices of the animal body, or when volatilised and transformed into arsenious acid, it assumes highly poisonous qualities. Its effects are deleterious whether it be respired as dust, swallowed in a soluble form, or applied externally to the skin. Its escharotic properties have long been known. In miners employed in the extraction of arseniferous metals a form of pneumonia, which rapidly becomes purulent, has been observed; ulceration of the skin and mucous membranes is also met with. A large proportion of the men engaged in the arsenic reduction works close to the mines in Cornwall suffer from skin eruptions known as "arsenic pock," and from bronchitis, which paves the way for more serious lung disease. The ill-health of these workmen formed the subject of an inquiry, and was reported upon to the Home Office in 1901 by Messrs. E. Gould and J. S. Martin. Many of the symptoms complained of by zinc-smelters are due to the presence of arsenic in the fumes. Of the miners of Schneeberg in Saxony, who extract cobalt ores—minerals composed mostly of nickel and bismuth—3 per cent die annually from a disease locally known as "cancer of the lung," a chronic affection probably due to the presence of arsenic in the cobalt; and in our own country the men who are engaged in colour works, where emerald green, a mixture of arsenic and copper, is made in large quantities, occasionally suffer from sores of the skin—particularly in the axilla and groin, along

the sides of the nails, and on the penis. These are caused by the dry dust which settles upon the skin and erodes it; the evil is aggravated by friction of the clothes, by the presence of perspiration, or by handling of the genital organs during micturition with fingers covered with the green dust. Ulcers on the penis of workmen engaged in making emerald green have been wrongly attributed by their wives to other causes. In this country the dangers consequent upon the manufacture of arsenic have been much diminished by improved ventilation, the use of a fan, and by what is technically known as the "wet method." I have visited the emerald green manufactories in England and examined many of the workmen; and although I admit that skin eruptions and ulcers occur, they do so far less than the public have been led to suppose. Men and girls who are employed in the making of artificial flowers, or of toys dusted with Scheele's green mixed with other pigments—with chromate of lead, for example—suffer from diffuse erythema, minute vesicular eruptions becoming pustular, ulceration, and gangrene of the skin. The eruptions are noticed mostly at the bends of the fingers, elbows, and arms, the angles of the nose and lips, the inside of the thighs, and between the toes. Persons with open sores on their hands and arms ought to have these protected when at work with gloves, and painful fissures of the skin should be coated with surgical collodion. Several of the bright red colours used as pigments in the arts and commerce contain arsenic; for example, cochineal red, Persian red, vermilionette, and rosaniline.

The occupation of rooms lined with wall-papers containing arsenic has frequently been followed by a series of symptoms, the real nature of which was long unrecognised. In 1839 Gmelin called attention to the danger, and Kramer in 1852 instituted experiments to determine whether a volatile arsenical compound could be liberated in the circumstances. It was reserved for Halley in 1858 to record the first fatal case of poisoning attributable to this source. Of the pigment present in the wall-paper as much as 59 per cent was arsenite of copper. Besides the arsenical dust that falls from these wall-papers it is maintained that arseniuretted hydrogen or arsine is evolved—a gas which arises from the contact of arsenious acid with organic matter, the long-continued inhalation of which is dangerous. Removal of the patient from such a room is generally sufficient to effect a cure. Considerable doubt has been expressed in regard to poisoning from arsenicated wall-papers, and numerous experiments have been undertaken to solve the question. The symptoms have been attributed to the absorption of dust, to the inhalation of arsenical gas, or to the combined action of the two factors; but lately improved bacteriological methods in the hands of Selmi, Hamberg, Gosio, and Sanger have demonstrated that a volatile arsenical compound is formed by the action of certain moulds on organic matter containing arsenic. Taking potato pulp containing 0·5 to 1 per cent of arsenious oxide, and exposing it to the air of a cellar, Gosio found an abundance of mould upon it in a few days, and an intense garlicky odour was emitted. Pure cultures were made from this growth on sterilised arsenical preparations;

but the peculiar odour was only noticed from such organisms as the *Aspergillus glaucus* and *Mucor mucedo.* On decaying paper Saccardo found the *Penicillium brevicaule*, a mould so peculiarly sensitive to arsenic that Gosio has proposed to utilise it as a means of testing for arsenic in toxicological work. All micro-organisms may have a slight action in the course of time; but there are a few arsenio-organisms whose operation is immediate and intense. Of these *Penicillium brevicaule* stands out as the most sensitive, and it can be employed for the detection of arsenic in the presence of large amounts of organic matter. By this interesting and extremely delicate micro-biological method one part of sodic arsenite in 1,000,000 may be detected in a milk culture.

Arsenical poisoning has frequently followed the application of quack ointments to the skin for cancer; and the liquid in which fly-papers have been soaked has been used for criminal poisoning—the active principle of the brown *papier moure* being arsenious acid. The presence of arsenic in soot explains why sweeps and gardeners suffer from the external manifestation of cancer in larger numbers than men engaged in other occupations. Occasionally bismuth subnitrate contains traces of arsenic, the power for harm of which should not be forgotten in a medico-legal inquiry. Serious consequences have also followed the wearing of garments or gloves dyed with arsensical green. Fowler's solution contains 4 grains of arsenious acid to the ounce, and is an excellent remedy for chorea. It should be carefully administered, however; for when given in rather large doses, or for too long a time, it has frequently caused peripheral paralysis, bronzing of the skin, and ulceration of the intestine. Arsenic in the form of cacodylate of soda has been administered hypodermically and with benefit in tuberculosis, but occasionally excessive doses have been followed by sanguineous effusion at the site of the puncture, and by petechial hæmorrhages elsewhere. Arsenious acid is largely employed by dentists to destroy the nerve in decayed teeth; its employment is not wholly free from risk, seeing that the quantity used is never weighed by the dentist; but the quantity placed in the tooth cavity is usually very small, probably not more than $\frac{1}{20}$ grain. Arsenic, we know, does not form an albuminate; thus it is that it forms such an excellent paste for dental purposes; it can penetrate into all the recesses of a carious tooth. Plants soon wither if placed in a solution of arsenious acid; and if they have been grown on soils containing small quantities of arsenious acid infinitesimal traces of the metal may be found in their tissues.

Certain animals, such as partridges, are said to be refractory to arsenic. We do not know whether or how far the eating of the flesh of animals that have ingested arsenic may be followed by ill effects in man. The risk would be less in eating the flesh than the internal organs. Strychnine has been found in the muscles of fowls. The "aqua tofana," once renowned as the means adopted by a secret society of women for the wholesale poisoning of married men, was made by rubbing white arsenic into pork, exposing it to the sun for several days, and collecting

the liquor as it drained away. This fluid is not only extremely poisonous, but is also said to defy chemical detection. Its virulence probably depends upon a mixture of arsenites of cadaverine, putrescine, and some unknown ptomaines.

Arsenious acid is a strong poison to nearly all forms of animal life—from the highest to the lowest; the symptoms vary according to whether the poison has been inhaled as vapour, drunk in a soluble form, or applied externally; the condition of the health and the habit of the individual at the time are not without their influence. Von Tschudi, in 1851, drew attention to the practice of arsenic-eating by the mountaineers of Styria, Hungary, and certain parts of the Punjab; the belief in these districts being that under the influence of the drug the respiratory power is increased, and the complexion, particularly of the women, improved. We are familiar with its beneficial influence in certain forms of skin disease and in asthma; and although it is maintained that the Styrian peasantry, beginning the practice with small doses, gradually increase it to 30 grains, considerable doubt has been expressed concerning the practice; especially as we are told that the people who thus indulge live to a great age. Certainly a tolerance to the drug can be established. Half a grain of arsenious acid, for example, is a dangerous dose to give to a dog; yet a mongrel Scotch terrier of mine took more than a grain of arsenious acid daily for several months. Under its employment in smaller doses an intense stimulus was given to nutrition. The animal gained considerably in weight, became sleek and well covered, and the hair of its coat, which was thick, coarse, and stumpy, became long and silken. All who saw the dog were struck by the improvement in its appearance, particularly as regards its pelt. Arsenic has long been given by grooms to horses with their food to improve the coat and render them plump and well conditioned. Once begun, however, the practice has to be continued; otherwise the animal shews signs of falling off. It has been stated that in man no tolerance of the drug is established, and that the stories of the Styrian arsenic-eaters are purely imaginary. Tschudi's statements have been severely questioned. Dr. Parker of Nova Scotia reports the death of a male arsenic-eater who had taken from 2 to 3 grains of the drug daily for five months in the hope of relieving dyspepsia. When he discontinued it he found he was not so well. He stated that the skin was not improved by it, and that it had no appreciable effect upon the respiratory organs, nor upon the muscular system, which remained well developed; but he thought that the genital organs were stimulated by it. However, symptoms pointing to an extremely irritable state of the gastro-intestinal tract set in, followed by thirst, suppression of urine, collapse, and death. In this case the daily use of the drug did not beget any enormous tolerance of it in the economy—a circumstance quite in keeping with the opinion of Christison, that whilst the system may become habituated to the use of some of the organic poisons, habit does not diminish, but increases the activity of inorganic poisons entering the blood. The publication of Parker's case

drew from Dr. Craig Maclagan (in the same journal a month later) a paper giving an account of his travels through Styria, and of his personal observation of the practice of eating a mineral substance "Huttereich," known to be arsenic, which was locally asserted to render respiration easy during mountain climbing, and to act as a condiment and tonic; its more immediate effect on the system is to make the people lively, combative, and salacious, to which latter circumstance was attributed "the inordinate number of illegitimate children in some of these places, the proportion sometimes rising nearly as high as 60 per cent of the total births." Dr. Maclagan was an eye-witness of the practice of arsenic-eating in the case of two men, one aged twenty-six and the other forty-six years of age. To one of these men 6 grains were given on a piece of bread. This was swallowed, for the mouth was carefully examined afterwards and found quite clear. No immediate effects followed, but on examination of the urine arsenic was found therein. Whilst admitting that arsenic-eating is not in any sense of the word a universal habit amongst the Styrian peasantry, or even freely indulged in by the male population, Dr. Maclagan maintains "that decisive evidence has been brought forward not only to prove that arsenic is well known and widely distributed in Styria, but that it is likewise regularly eaten in quantities usually considered sufficient to cause immediate death." In 1875 Dr. Maclagan published a second paper describing, on the authority of Knapp, a public exhibition of arsenic-eating by two men, and mentioning that other cases were known to him. Knapp is of opinion that only strong persons can indulge in the practice, but that these attain great age; that the virtues claimed for arsenic exist; that the drug is taken at intervals of a few days, and that there is no longer any doubt about the arsenic-eating in Styria. A Royal Commission has reported that although the practice exists it has been grossly exaggerated.

I have been directly informed by Dr. Eberstaller, the town's physician of Gratz, that the practice of arsenic-eating was unknown to him, but that Marik, in a paper read before the Styrian Medical Society, had revived professional interest in this important matter by bringing to light nine cases of arsenic or *hidri* eating—four in Deutsch-Landsberg, two in Oberwölz, two in Vorau, and one in Ligist. Moreover, it was stated that there were two arsenic-eaters at Houtberg, and one each at Grafenberg and Raindorf. Of the nine cases one was a man aged sixty-six, who began eating arsenic at the age of thirty, and whose father—also an arsenic-eater—had died at the age of seventy-seven. In the presence of Drs. Knapp and Buchner this man took 2·16 grains of orpiment (arsenic trisulphide), and stated that he became an arsenic-eater at first under the belief that the drug was a prophylactic against typhus fever. Beyond an indisposition of two days' duration he had never been ill during these thirty-six years. When feeling lazy and disinclined to work he would take a small quantity of arsenic, and in a few hours would feel invigorated, and fit for a long pedestrian journey.

He maintained that sexual potency is rather increased by it than otherwise, and that after taking arsenic he must eat some food. The other arsenic-eaters were reported to be strong healthy men, who had indulged in the drug for periods varying from eight to twenty years. In the urine of four of these persons Buchner proved the presence of arsenic, both qualitatively and quantitatively; in one instance 0·385 grain being found. Marik therefore maintains that arsenic-eating is still practised in the north and north-western parts of Styria; and that, according to Schäfer, the practice is not unknown to peasantry of the districts of Hartberg, Lamprecht, Leoben, and Oberzeiring. It is difficult to obtain accurate information as to the number of arsenic-eaters in Styria, for the people know that the practice is illegal, and the greatest possible secrecy is observed. The practice has by no means died out, and the reasons assigned for taking the drug are still the same as they were many years ago; namely, that it gives strength and vigour to the muscular system, increases the respiratory power, aids digestion, and is a prophylactic against infectious fevers. Believing that it acts as a cosmetic, it was used by young ladies in the upper classes of society in Florence some years ago.

Morbid Anatomy.—No matter by what channel arsenic has entered the system, the mucous membrane of stomach and intestines is the seat of very marked changes: it is swollen and congested; it may shew numerous ecchymoses, small emphysematous bullæ, or membranous exudation. The œsophagus generally escapes. If arsenic has been taken in the solid form, crystals are frequently found adhering to the mucous membrane. Long after death, months it may be, the inflammatory changes of the mucous membranes can be recognised owing to the antiseptic and preservative powers of the drug; but care must be taken to discriminate between this and the peculiar redness observed in normal stomachs undergoing putrefactive changes. The whole of the intestinal tract in arsenical poisoning may be so reddened that the lesions may closely resemble those of cholera; a resemblance which even microscopical examination does not remove, for equivocal micro-organisms have been found in the epithelial flakes. Fatty degeneration of the intestinal epithelium and a swollen condition of Peyer's patches and of the solitary glands may also be present. Arsenic has thus a peculiarly selective influence upon the gastro-intestinal tract. That the lining membrane of the stomach actively excretes certain chemical bodies has been shewn by Kandikoff of St. Petersburg, who demonstrated that if arsenic, for example, were injected into the rectum it was absorbed and subsequently discharged by the mucous membrane of the stomach. To kill an animal by means of arsenic, a larger quantity has to be injected into a vein than if the drug is given by the mouth. The explanation of this peculiar behaviour of arsenic is probably that when the drug has been absorbed into the blood it is separated by the gastric mucous membrane, and in its passage outwards it exercises an irritant action, setting up inflammatory redness.

A widespread fatty granular degeneration, again, is characteristic of arsenical poisoning. It affects the liver and kidneys, the intestinal epithelia, and voluntary muscular fibre. The degeneration is sometimes as marked as that met with in phosphorus poisoning. Binz considers that cellular protoplasm has the power of oxidising arsenious to arsenic acid, which is again reduced to arsenious acid. In this way, owing to a series of repeated oxidations and reductions, the protoplasm undergoes a fatty change. There are no observations to support this opinion. Arsenic uniting with protoplasm may not form an albuminate, yet it enters into such close chemical union with it that the protoplasm is destroyed. Besides the widespread fatty change in the liver, Salkowsky found that its glycogenic function was destroyed; but in my experiments glycogen was found in the liver after death.

Whilst arsenic is rapidly eliminated from the system, the channels of escape being the gastric mucous membrane, kidneys, skin, and saliva, sufficient is yet retained within the system to allow of its detection post-mortem; although fatal cases of arsenical poisoning have been recorded without the metal having been found. This is a point of considerable importance from a medico-legal point of view. In the case of my own dog, which took arsenic every day for months, and which before its death suffered from vomiting, diarrhœa, and rapid emaciation, the most careful chemical examination of the liver and bones conducted by Professor Bedson and Mr. F. C. Garrett, repeated on three occasions, failed to detect the slightest trace of arsenic. This is a circumstance of more than passing interest. In cases of criminal poisoning, therefore, there is no justification for the plea set up by the defence, that unless an amount of poison were abstracted from the liver, sufficient of itself to be regarded as a fatal dose, the cause of death could not have been arsenical poisoning. Arsenic has been detected in the bile, the sweat, the tears, and in the serosity of a blister; but the urine is the medium by which it principally escapes from the body, hence the improbability of any extensive accumulation of arsenic. Given, therefore, a case of suspected poisoning by arsenic, the urine of the patient should be examined by Reinsch's test. In using this method the following points should be attended to: (*a*) reduce 12 to 16 ounces of urine by gentle evaporation to $\frac{1}{4}$ of its bulk; (*b*) add $\frac{1}{6}$ to $\frac{1}{5}$ of its bulk of *hydrochloric acid known to be free from arsenic*; (*c*) dip into it a bright piece of copper foil and boil for at least 15 minutes, when (*d*) if arsenic be present the copper will exhibit a greyish stain. If arsenic be present in large quantity a glistening black-lead appearance may be obtained; but, as mercury, sulphur, selenium, and antimony produce a similar effect, the copper foil must be submitted to the test of sublimation. Should the stain be due to mercury, the metal sublimes in microscopic globules; if to sulphur it will rub off upon the finger; if to arsenic it dissolves in caustic ammonia, which sulphide of copper will not do. The arsenical stain, when sublimed, gives a crystalline deposit of arsenious acid; the antimonial stain is bluer and gives no crystalline sublimate.

In poisoning by white arsenic a microscopical examination of the vomit may be of considerable assistance. Numerous small white particles are frequently observed which, when picked out by the forceps, carefully washed, dissolved in boiling water, and allowed to cool, crystallise out as small octahedra of arsenious acid. From these when heated with soda on a piece of carbon in the reducing zone of the flame of a blow-pipe a garlicky odcur is evolved. For fuller details of the longer and more accurate methods of testing for arsenic in organic substances known as Reinsch's or Marsh's, the reader should consult text-books on toxicology.

Into the question of the imbibition of arsenic after death we need scarcely enter, there being few arguments and fewer facts to support the assumption. In courts of law it has been maintained that corpses may absorb arsenic from the earth—the hypothesis being that though arsenic in the soil is in the form of an insoluble compound, it might combine with calcium to form the arsenite of lime, which, becoming soluble through the action of carbonic acid evolved from decaying vegetables, might filter down to the corpse. Sonnenschein's experiments indicate the improbability of such an occurrence.

Symptoms.—When administered in small doses arsenic acts as a tonic by gently irritating the stomach, thereby provoking appetite. It exercises a distinct influence upon nutrition, improving muscular tone and creating fresh vigour.

Poisoning by arsenic may be acute or chronic. Arsenic—white arsenic or arsenious acid—is soluble in water, has a faint sweetish taste, and when volatilised emits a strong garlicky odour. It is an escharotic when applied to any surface in a concentrated form, and an irritant even when diluted. From a quarter to half an hour after taking a large dose a burning pain is felt in the œsophagus and stomach, which spreads over the whole abdomen, and is accompanied by a sense of constriction at the throat and a metallic taste in the mouth. Consequent upon the intense intestinal hyperæmia are violent purging and vomiting; the discharges, at first mucous, become bilious and tinged with blood as in English cholera. Thirst becomes excessive, the urine is suppressed, arterial pressure falls, and the patient soon becomes collapsed and his extremities cold; the abdominal tenderness renders respiration laboured and embarrassed. Gradually, however, the pale face becomes cyanosed, cramps keep recurring, the temperature falls, convulsions or coma supervene, and death follows in from five to twenty hours. There is a close resemblance between such a case and cholera; and were the latter epidemic at the time, and nothing present in the circumstances to excite suspicion, such a case, even in the hands of an experienced physician, might be mistaken. In some cases there is only a profuse watery intestinal discharge; and whilst during life the case closely resembles cholera, the suspicion is not dispelled by the appearances presented at the autopsy.

A more common form of poisoning is the subacute. The symptoms

of slow arsenical poisoning are of a milder character, and are remittent. The vomiting and purging may intermit, and the abdominal pain may subside, although it is still present on pressure. The other characteristic symptoms are persistent thirst and painful deglutition; scanty urine, red in colour, and frequently albuminous; heart weak and irregular; abdomen tumid; face cyanosed; skin cold and clammy, and exhaling the peculiar odour of arseniuretted hydrogen; the legs drawn by cramps and convulsions, whilst the mind, as a rule, remains perfectly clear. From time to time there is a remission of the symptoms, the patient rallies, and there is hope of recovery; but the improvement is not maintained, the symptoms recur, and death ends the scene. Towards the end hiccup is not uncommon.

A single large dose of arsenic may prove quickly fatal; or it may cause a prolonged illness which may end fatally, the origin remaining obscure. Such was the case for a period when, in 1900, an epidemic of peripheral neuritis suddenly appeared in the Midlands. Dr. E. S. Reynolds of Manchester traced the malady to beer and porter-drinking. Women suffered more than men. As the symptoms at first began with numbness and sensations of pain in the hands and legs and burning in the soles of the feet some of the patients were thought to be suffering from erythromelalgia; but in others the symptoms of peripheral neuritis were well marked from the commencement. Frequently the skin was deeply pigmented all over, the appearance of the patient being such as to recall Addison's disease, or it was the seat of a scarlatinal or measly eruption which desquamated, of herpes zoster, keratosis, blisters, or of ulcers. In many of the patients the face was puffy and pigmented, there was ankle-drop due to paralysis of the anterior tibial muscles, the feet were swollen, and there were signs of heart failure without cardiac murmurs. In the worst cases the arms and legs were paralysed and the muscles atrophied; occasionally the muscles of the trunk became paralysed, as also the diaphragm. Dr. Dixon Mann found arsenic in the beer in varying quantities, the source of which was ultimately shewn to be the glucose and sulphuric acid used in the manufacture of the beverage.

If arsenical poisoning be not followed by death convalescence is slow, and is apt to be retarded by various disorders, principally of the alimentary canal; or nervous symptoms connected with motion and sensation may appear, such as anæsthesia, hyperæsthesia, loss of the thermic sense, and paralysis. Joubert-Gourbeyre collected 100 cases of arsenical poisoning, and in more than one-half all the extremities were affected; one-fourth were paraplegic, in the remainder there was hemiplegia or some limited form of paralysis. The loss of power was mostly limited to parts below the knee and elbow. Arsenical paralysis, like that due to alcohol, usually begins in the legs. On the occurrence of paralysis the muscles undergo rapid atrophy, are usually sensitive to pressure, and at an early date present the "reaction of degeneration." These symptoms are usually met with when arsenic has been taken for a long period; but Meirowitz reports

the case of a young man aged nineteen, who inadvertently swallowed 5 grammes (77 grains) of arsenious acid. This was followed by extremely severe symptoms of acute arsenical poisoning; they subsided, and three weeks afterwards his legs became painful and his feet swollen; these symptoms gradually increased until he was unable to walk without crutches. Subsequently his gait became ataxic, and his feet cyanosed and cold; the muscles of his legs atrophied rapidly, and were painful on pressure: the calf-muscles were the seat of involuntary twitchings; the foot, patellar, and cremasteric reflexes were absent; the soles of the feet were anæsthetic, whilst the skin of the lower half of the legs was hyperæsthetic, with deficient response to the faradic and galvanic currents. The hands were also affected, the movements of the fingers being greatly impaired. The symptoms of multiple neuritis occurred two months after the swallowing of a single large dose of arsenic.

Arsenical multiple neuritis in some respects resembles subacute polio-myelitis; but there is more pain, and the combination of sensory disturbance and tendency to rapid cure diminishes the resemblance. Is the lesion peripheral or central? Wood alludes to the experiments of Popoff, who found in dogs, killed in a few hours by arsenic, the spinal cord inflamed; and in cases of slower poisoning that the small blood-vessels in the cord were thickened, the protoplasm of the large multi-polar cells opaque and granular, and their nucleus indistinct: subsequently the cells became vacuolated. Erlicki and Rybalkin found disease in the anterior horns of the grey matter and in the peripheral nerves; and they maintain that myelitis, and particularly changes affecting the multipolar cells, are consequences of arsenical poisoning. Whilst the alterations were well marked in the cord on microscopical examination, there had been no tenderness along the course of the nerves during life. As in lead poisoning, it would appear as if the lesion might be peripheral or central, or a combination of both.

The administration of arsenic for a long time, even in small doses, must induce changes in the nervous system. Arsenic deranges the function of nerve-fibres particularly, for these appear to be more susceptible than nerve-cells, and altered function is followed by altered structure. In metallic poisoning one is struck by the bilateral symmetry of the peripheral nervous lesions, and that certain fibres, motor or sensory, are more affected than others. Again, there may be a simulation of tabes, with ataxia, muscular anæsthesia, and loss of knee-jerk, consequent upon a preponderant affection of the afferent nerves. How peculiarly susceptible nerves are to all toxic influences has been shewn by Sklaret of Berlin, Ringer and Murrell. On injecting arsenious acid or an arseniate into animals, they found that the drugs acted directly upon the nerve-centres, producing paralysis of motion with loss of sensation and reflex action, and that they were highly toxic also to the peripheral nerves.

Different organs exhibit a selective influence in regard to arsenic. In acute poisoning this is seen in the gastric mucous membrane; and in chronic forms in the liver, kidneys, and heart. The skin is affected

in chronic arsenicism. In the treatment of chorea by increasing doses of Fowler's solution, whilst the disease may be cured, there is frequently left after it deep brown pigmentation of the skin, either of the face especially, or spread generally over the trunk and limbs—a pigmentation which does but deepen under the administration of potassium iodide, given in the belief of its being an eliminant for arsenic. Arsenic is said to prevent the acne of bromism; but, if this be so, yet such patients may present mild pigmentation—first as discrete small spots which ultimately coalesce.

Sex is not without its influence in the evolution of the symptoms. Cox investigated 1700 cases treated by arsenic and found that the gastric symptoms are commoner in women, and the intestinal in men; that the conjunctivæ are often inflamed in men, and that nervous symptoms are more frequently observed in women. Children and young people bear arsenic well; but old people are peculiarly susceptible to it, and in them signs of nerve degeneration rapidly appear.

When arsenic is administered in small doses for a long time the symptoms may be slight; the health is so gradually deteriorated that disease from other causes is simulated: in other cases the slow form of poisoning is but a repetition in miniature of the acute. There may be gradual loss of appetite, emaciation, increasing feebleness, depression of spirits, irritability of temper, sleeplessness, pigmentation of skin, conjunctivitis, catarrh of the nasal mucous membrane, scanty urine, numbness of the extremities, hyperæsthesia, paralysis, convulsions, fainting, and death.

Mr. Jonathan Hutchinson noted the influence of arsenic in causing keratosis of the palms and soles in a young lady the subject of lupus, in whom the keratosis gradually disappeared on discontinuing the medicine; he also reported the case of a young man who, after taking arsenic for eight years, developed numerous small corns and a peculiar horny condition of the palms and soles, which on microscopical examination shewed great thickness of the epidermis, but no disease of the papillæ. There is now a considerable amount of evidence to shew that in addition to peripheral neuritis, bronzing of the skin, and the development of keratosis, the prolonged administration of arsenic may be productive of even more serious consequences. Further, he alludes to a case of Mr. Arbuthnot Lane's—a man who, after taking arsenic for thirty years in order to relieve psoriasis, became the subject of multiple growths of squamous-celled carcinoma. Professor Allbutt has seen a similar result in a young woman. It appears that the keratosis and multiple small growths that develop in the skin after a lengthened course of arsenic are peculiarly prone to take on malignant action. Whilst, therefore, arsenic causes marked thickening of the skin it is indirectly responsible for growths which subsequently become true cancer. It may also cause other forms of skin irritation. Wood mentions a case of obstinate eczema of the hands consequent upon using playing-cards containing on the back one-eighth of a grain of arsenic each.

The diagnosis of chronic arsenical poisoning is at times extremely difficult. Peripheral neuritis and progressive emaciation, without local disease, are either diathetic or toxic. A chemical examination of the urine may throw light upon a doubtful case.

Treatment.—If the case be acute and seen early, emetics and the use of the stomach-tube are called for; but the antidote for arsenical poisoning, when the drug is still present in the stomach, is freshly prepared ferric hydrate. It acts by converting soluble arsenious acid into the insoluble arseniate of iron. Ferric hydrate is rapidly prepared by adding liquor ammoniæ fortior to the liquor or tincture of the perchloride of iron, care being taken not to add excess of ammonia. The liquid may be administered without filtration and given freely. Should the poison have already passed into the system ferric hydrate is useless. The treatment must then depend upon the symptoms. Copious draughts of water probably aid the elimination of the drug by the kidneys. For arsenical paralysis tonics such as liquor strychninæ may be necessary; as well as the employment of massage and electricity. Iodide of potassium may be of service as an aid towards the elimination of the poison in mild subacute cases.

THOMAS OLIVER.

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